

Section 4)

**Attachment no. 2**

C.R.F. S.p.A.:

Subacute Toxicity of Fructose-1,6-Diphosphate,

1976

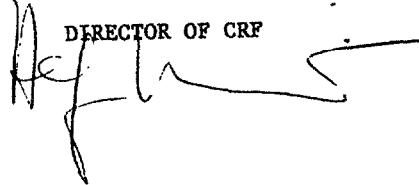
VOL. II



**CRF** centro ricerca farmaceutica  
s.p.a.

NON CLINICAL LABORATORY INSPECTION DATA  
OF THE STUDY CRF 026

Dr. ALFREDO NUNZIATA

DIRECTOR OF CRF  


AUTORIZ. MIN. SAN N. 8002/70.273/28258 DEL 3/8/74 - N. 8002/70.273/26860 DEL 12/3/76

VIA TITO SPERI, 14 - 00040 POMEZIA (ROMA) - TELEFONO 9120648 - 9121085  
CAPITALE SOCIALE LIRE 1.000.000.000 - C.C.I.A. N. 375736 - REG. SOC. TRIB. DI ROMA N. 2828/7



**CRF** centro ricerca farmaceutica  
s.p.a.

STATEMENT OF C.R.F.

The toxicological study of CRF 026: Esafosfina<sup>R</sup> - Subacute toxicity of one month in Beagle dog has been performed by our Centre from 12/5/1976 to 7/10/1976.

The researchers of various departments are:

TOXICOLOGY

Piero Mercatelli (B.Sc.)

HISTOPATHOLOGY

Alberta Argentino-Storino (B.Sc.)

BIOCHEMISTRY

Renato Ottavio Salerno (B.S.)

TECHNICAL DIRECTOR - MINISTERIAL EXPERT

Alfredo Nunziata (PHD)

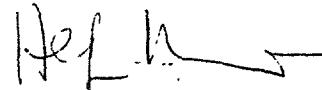
SCIENTIFIC DIRECTOR

Giulio Cesare Perri (MD. PHD.)

The "Curricula Vitorum" of the above-mentioned are enclosed.

All the original documents, the specimen, the slides and all the material concerning this experiment are available for inspection in our own files at the following address:

C.R.F. S.p.A. - Via Tito Speri, 14 - Pomezia - Rome - Italy.

  
Centro Ricerca Farmaceutica S.p.A.  
Dr. Alfredo Nunziata

AUTORIZ. MIN. SAN. N. 800 2/70.273/28258 DEL 3/8/74 - N. 800.2/70.273/26860 DEL 12/3/76

VIA TITO SPERI, 14 - 00040 POMEZIA (ROMA) - TELEFONO 9120648 - 9121084 - 9121085  
CAPITALE SOCIALE LIRE 500 000.000 - C.C.I.A. N. 375.736 - REG. SOC. TRIB. DI ROMA N. 2828/7

Study C.R.F. 0.26: 30 DAYS SUB-ACUTE TOXICITY IN DOGS (1976)

Daily registers: They show weights and dietetic consumptions registered during the test. Some corrections are signed and dated.

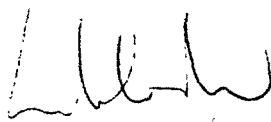
File: It contains the protocol with the notes for the corrections of the doses administered before the experiment, dated and signed delivery notes and analytical certificate of product in question.

Raw data: Drafts of reports, copies of tracks and autoptic cards.

Specimen: The reports are filed with experimental number, group and animal numbers.

Roma, 15.5.1982

R. Costrini



Nonclinical Laboratory Inspection Data

A. TESTING FACILITIES

1. The testing facility in general is of suitable size, adequate construction and properly located to perform nonclinical laboratory studies. Defined and, if necessary, separate areas are provided.

Yes - plan of laboratories and facilities are enclosed.

2. Adequate space is provided for administration, supervision, and direction of the testing facility as well as satisfactory facilities for toilets, lockets, showers with hot and cold water, and air driers or single use towels plus all necessary accouterments in accordance with regulations set forth by the OSHA in 29 CFR.

Yes.

B. PERSONNEL

1. List of personnel at the date of test in February 1976:

Director	:	Prof. G.C. Perri
Associate	:	Dr. A. Nunziata
Researchers	:	Dr. P. Mercatelli : Toxicologist
		Dr. A. Argentino : Pathologist
		Mr. R. Salerno : Biochemist
		Mr. T. Bianco : Chemical Analyst
		Dr. M. Nannini : Toxicology
		Technician
		Dr. R. Campa : " "
		Mr. G. Magnarelli : " "
		Miss. L. Cancelli : Toxicology worker
		Mrs. T. Fusco : " "

Mr. A. Lupi : Toxicology worker  
Mr. M. Paciarotti : " "  
Mr. V. Delfino : " "  
Mrs. A. D'Antona : Histopathology worker  
Dr. M. Monaco : Mutagenetist  
Dr. V. Ortali : " "  
Mrs. A. Dello Russo : Mutagenesis worker  
Mrs. T. Brustolin : " "  
Mrs. I. Di Filippo : " "  
Mrs. M. Tranquille : Scientific Secretary

2. Employees practice good sanitation and health habits.

Yes in respect of Italian laws.

3. Employees follow standard operating procedures for health and safety and have adequate laboratory clothing appropriate for their duties and to prevent microbiological or chemical contamination of the test substance.

Yes in respect of District Regulations. Such operating procedures are not written.

4. All employees are instructed to report to supervisory personnel any and all health or medical conditions that may be considered to adversely effect the study.

Yes at the moment of the agreement and periodically depending from the type of protocols.

C. QUALITY ASSURANCE UNIT

1. There is a quality assurance unit (QAU).

QAU in Italy in 1976 was called Responsible of Ministry of Health and he was Dr. Alfredo Nunziata.

2. A master schedule sheet of all nonclinical laboratory studies is maintained by the QAU.

Schedule sheet was maintained in a central file.

3. Copies of all protocols and standard operating procedures are maintained by the QAU.

Yes

4. Critical reviews of final reports are made to assure accuracy of description with respect to methods; and,

Yes critical reviews of final reports were made by the Scientific Director and Responsible of Ministry of Health.

5. Standard operating procedures; and,

Critical reviews were made by people in C4 using all materials.

6. Observations; and,

Critical reviews were made by people in C4 using all materials.

7. Raw data; and,

Critical reviews were made by people in C4 using all materials.

8. Results (assuring that all adverse findings are indeed included in the final report)

Critical reviews were made by people in C4 using all materials.

9. Procedures are written that describe the responsibilities of the QAU and the records it maintains.

Responsibilities of the QAU (Responsible for Ministry of Health) are written in Italian Ministry of Health Circular 54 bis and 75.

D. EQUIPMENT

1. Equipment of appropriate design and adequate capacity is available to obtain values reported.

Yes.

2. Location of equipment permits easy operation, cleaning and maintenance; and,

Yes.

3. Is cleaned, inspected and maintained regularly.

Yes.

4. There are written standard operating procedures which describe in detail the methods, materials and schedules to be used in the routine inspection, cleaning, maintenance, testing and calibration of equipment; and,

Procedures for equipment in respect of the procedures of the suppliers for cleaning etc. are not written procedures but only internal regulations and control of Head of Laboratory.

5. The specific remedial actions to be taken in the event of failure or malfunction of equipment; and,

Yes.

6. Designates the individual responsible for each of the operations.

Yes for each laboratory the Head is the individual responsible.

7. Copies of the standard operating procedures are available to laboratory personnel.

References of the methods and procedures are available to laboratory personnel.

E. TESTING FACILITY OPERATION

1. Separate laboratory space is provided for the performance of routine procedures or categories of procedures; and,

Yes.

2. Separate laboratory space is provided for the performance of specialized activities such as aseptic surgery, intensive care, necropsy and radiography

Yes.

3. Spaces of cleaning, sterilizing, and maintaining equipment and supplies used during the course of the study are separate from the areas housing the test system.

Yes.

4. Studies involving radioactive or other biohazardous materials are carried out in special facilities or areas which provide protection to personnel, test systems, and the external environment against contamination or unnecessary radiation exposure, or infection.

Yes.

5. Persons possessing and using radioactive materials are licensed in accordance with the Nuclear Regulatory Commission regulations or meet the requirements of an agreement state.

Yes.

6. Special procedures are employed for the handling of other biohazardous materials.

Yes in respect of the Italian laws.

7. Written standard operating procedures (which at least meet GLP requirements) are maintained detailing the methods to be used in performing non clinical laboratory studies.

No. Detailed methods were written or photocopy of references was made available.

18. Preparation and validation of final study report.

Idem as E10.

19. A historical file of standard operating procedures annotating effective dates and dates of revisions is maintained.

No data are only available for all materials of the study that are kept in the archives or in a general file.

20. The relevant standard operating procedures are available at all times in the immediate bench area of personnel performing the procedures.

Idem as E19.

21. All reagents and solutions in the laboratory area are labeled adequately.

In respect with Italian regulations.

F. ANIMAL CARE

1. The testing facilities which utilize cats, dogs, guinea pigs, hamsters, rabbits, or nonhuman primates have been inspected by the U.S. Department of Agriculture Animals Plant Health Inspection Service, and found to be in compliance with the Animal Welfare Act of 1970 (9CFX Part 3) within the past 2 years (Indicate date and results; and/or

Not only by the Italian Ministry of Health

Physician of the Province

Veterinary of the Province

ENPI

Ispettorato del lavoro

2. Feed and water used for animals are analysed periodically for the presence of known interfering contaminants.

Suppliers certified the quality of water (District Administration) and that of food (Morini S. Polo d'Enza - Italy)

3. A program for adequate veterinary care and humane treatment has been established and is supervised by a doctor of veterinary medicine (INDicate name of DVM) for studies involving cats, dogs, guinea pigs, hamsters, rabbits, or nonhuman primates; and,

Veterinary care was made in respect of Italian regulations by Dr. P. Mercatelli and supervised by the Province and District Veterinary.

4. For studies involving other animals by either a doctor of veterinary medicine or by other qualified persons (indicate name and qualifications).

Idem as F3.

5. Animals either known to be, or suspected of being diseased, or carriers of a disease, are isolated in an area contiguous with or near the animal housing area.

Yes.

6. Animals are free of any naturally occurring diseases or conditions that might interfere with the purpose or conduct of the study.

Yes.

7. The diagnosis, authorization for and description of the treatment (including dates of treatment of animals involved) of test systems is adequately documented.

Only if it happens without written authorization.

8. Methods for the unique and permanent identification of all animals when needed have been developed and applied to preclude mixup of animals and/or their tissues; and,

Yes.

9. Routine of specialized housing of animals of different species, or of the same species used for different studies is adequate to preclude interspecies transmission of infection, mixup, or other events that may affect the outcome of a study or studies.

Yes.

10. The proper placement of animals which are transferred from one cage to another in the same location is checked by the transferer and verified by a responsible person appropriately documented, and a record of the procedure maintained.

No.

12. Animal waste and refuse is collected, stored and disposed of in a safe and sanitary manner so as to preclude vermin infestation, odors, and disease hazards.

Yes.

13. Animal cages, racks and accessory equipment are cleaned and sanitized at appropriate intervals as recommended in HEW Publication No. (NIH) 74-23 or subsequent revisions.

Yes.

14. Storage areas for feed, bedding, suppliers, clean cages, and equipment are separate from areas housing the test systems as well as the quarantine and isolation area, and these materials are protected against spoilage, infestation or contamination.

Yes.

G. TEST AND CONTROL SUBSTANCES

1. Each container for a test and control substance is appropriately labeled and adequately stored to maintain the identity, strength, quality, and purity of said substances.

It was labeled by the Sponsor and stored in cold room.

2. An appropriately identified reserve sample selected at random from each batch of test and control substance used in a study of more than 4 weeks duration, is taken, stored in an identical immediate container under appropriate storage conditions, and analyzed at the time the batch is depleted, at the termination of the study, or at the expiration date (whichever occurs first) to assure that the identity, quality, strength, purity, and stability conform to established specifications.

No.

3. If test or control substances are mixed with a carrier prior to administration each batch of such mixture is tested periodically for the adequacy of the mix to assure uniformity and to determine the concentration of the substance in the mixture. Describe procedures used.

No only at the beginning by the Sponsor.

4. Enough samples of each batch of the mixture are returned to the Sponsor for such analysis if the study is a blind study.

No.

5. Each batch of the test and control substance-carrier mix is tested for stability for at least the length of time between mixing and use and to establish storage conditions and an expiration date.

No.

6. For each batch of the test and control substance, tests are performed to determine the release from the carrier mix and the results documented.

No.

7. For each batch of test and control substance mixed with a carrier an appropriately identified reserve sample of each batch of the substance-mixture is taken and retained for the required length of time.

No.

8. All handling, storage and disposal of known or suspected chemical carcinogens used as the test substance in a study are treated in accordance with the safety principles set forth in the "National Cancer Institute Safety Standards for Research involving Chemical Carcinogens", HEW Pub. No. (NIH) 75-900.

Yes in respect of Italian regulations.

H. STUDY IMPLEMENTATIONS AND CONDUCT

1. Scientists or other professional persons are available to provide assistance and consultation to subordinates and to handle unforeseen issues.

Yes.

2. Specimens are identified by test system number, study number, nature of specimen and date. Explain identification system.

Yes. Specimens are coded either by test number date or animal number or code number depending of the specimen.

I. STORAGE AND RETRIEVAL OF RECORDS AND DATA

1. The testing facility maintains and retains all raw data, documentation and other information, protocols, specimens, and final reports generated during and as the result of a nonclinical laboratory study and they are retained in an archive of adequate space and design and are indexed to facilitate their orderly and expedient storage and retrieval.

Yes.

2. The archive provides the proper conditions to minimize deterioration of all stored material for as long as they are required to be retained.

Yes.

3. The archive contains specific reference to other locations in which documents and specimens may be stored.

All materials are kept in the archive.

4. Documents and specimens required to be maintained in the archive and not physically present there have appropriate and specific reference to their location filed in the archive.

Yes.

5. An individual responsible for the archive is identified.

Yes.

6. Only authorized personnel enter the archive and whenever a custodian of the archive is not present the suitable repositories for the documents and specimens are locked.

Yes.

7. Whenever the original material is transferred to the sponsor's archive at the sponsor's request at the completion of the study, duplicates of all material required to be in the archive are retained there, when the nature of the material permits.

Original material is never transferred to the sponsor's archive.

8. All material required to be retained in the archive is available for inspection to authorized employees of the Food and Drug Administration.

Yes.

9. If the archive has been contracted out to a commercial archive not belonging to the research facility or sponsor, then the name and address of the commercial archive has been provided to the sponsor in the submission of the final study report.

Not applicable.

J. RETENTION OF RECORDS

1. All protocols, raw data, specimens, final reports and other required documents pertinent to the conduct of the study, including records and reports of maintenance, cleaning, calibration and inspection of equipment, are stored in an archive, and retained for the specified time.

All materials pertinent to the study are kept in the archive.  
Time depends on the Sponsor request.

2. Curriculum vitae and job descriptions of all personnel engaged in conducting the study are retained for the specified period of time, either in the facility employment records, or the archive; and are available for inspection.

Data are kept in the administration office.

3. The master schedule sheet, records of inspection or evaluation and status reports of the quality assurance unit are retained for specified period of time.

No.

K. PERSONNEL

1. Adequate periodic training is provided by well-qualified individuals to assure that each person engaged in a laboratory study continues to be qualified for his/her function.

Personnel is examined by the Head of Laboratory and by Technical direction.

2. A current curriculum vitae (C.V.) is maintained along with a current job description for each person engaged in the conduct of the study. The testing facility also retains the last available C.V. and job description after termination of employment. (Obtain copies of C.V.).

Yes.

3. The testing facility has a sufficient number of personnel to accomplish the activities specified by the protocol.

Yes.

4. Persons found to have an apparent illness that may adversely affect the integrity of the study are removed from direct contact with any or all applicable aspects of the study until the condition is corrected. Such facts are documented in the records of the study.

Yes but these facts are not documented.

L. QUALITY ASSURANCE UNIT

1. Each phase of a study is periodically inspected, written reports are prepared, and corrective actions when required are documented.

Each phase of a study is not periodically inspected by the Responsible Ministry of Health.

2. All studies are evaluated for conformity to the protocol as required, deviations from the protocol or standard operating procedures are not made without prior approval, and written records of these activities are maintained. The quality and reliability of work performed by contractors and grantees is monitored.

Deviations are only written on the final report and on laboratory record.

3. Status reports are submitted to management periodically.

No.

M. EQUIPMENT

1. Equipment, procedures and materials used to protect the integrity and health of test systems, including pest control, are of appropriate design and type, and do not interfere with the conduct of the study; and,

Yes.

2. Can be easily cleaned and maintained; and,

Yes.

3. Is cleaned, inspected and maintained regularly.

Yes.

4. Equipment and materials used to prepare and administer test and/or control substances are of adequate design to assure accurate administration of these substances; and,

Yes.

5. To preclude contamination of test and control substances; and,

Yes.

6. Can be easily cleaned and maintained; and,

Yes.

7. Is cleaned, inspected, maintained and calibrated regularly.

Yes.

8. Written records are kept which accurately document all inspection, cleaning, testing, and calibrating operations; and,

No.

9. Nonroutine maintenance and remedial actions taken because of failure or malfunction.

Yes.

10. The use of all cleaning, maintenance, and pest control materials which might interfere with the conduct of the study or be hazardous to the test system is adequately documented and does not contaminate test systems.

Yes.

N. ANIMAL CARE

1. Needs for deviation from the standards for animal care are adequately documented and incorporated in the records of the study.

Not completely.

2. Environmental factors such as the caging and housing systems, sanitation practices, diet, handling, ventilation, lighting, temperature and noise control are maintained uniformly throughout the course of the studies; and,

Yes.

3. Changes to new locations, or of environmental factors, are not made during the course of the study without written permission from the study director; and the record of the approval and details of the changes are maintained.

Changes are not made during the course of the study.

4. All newly received animals are kept in quarantine for a predetermined period of time during which their health status is evaluated. (State length of quarantine period for species involved in this study and reasons for disqualifying animals from the study if applicable).

Animals (dogs) were kept in quarantine for 30 days in some area of the study.

5. Bedding used in animal cages or pens does not interfere with purpose or conduct of the study.

Bedding was not allowed in the pens.

O. TEST AND CONTROL SUBSTANCES

1. Each batch of a test and control substance is assayed for identity, strength, quality, and purity prior to initiation of the study either by the laboratory or the sponsor who provides verifying documentation with the substances.

These actions were performed by the Sponsor.

2. Prior to initiation of the study the stability of each test and control substance is determined, where possible, and if not previously determined by the sponsor, unless stability is the purpose of the study.

Idem as G1.

3. The test and control substances are derived from the smallest number of production batches consistent with their stability and necessary to fulfill the requirements of the study.

Test substance was derived from one batch.

4. A system for the distribution of the test and control substances is established with procedures to assure that proper storage at all times maintains the identity, strength, quality, purity, and stability of the substances; and,

Procedures were used "de facto" by verbal indication of the Head of Toxicology.

5. the possibility of cross-contamination of the substance, is precluded; and,

Yes.

6. appropriate identification of the substance is maintained throughout the distribution process; and,

Yes.

7. the receipt and distribution of each batch of the substance is properly documented.

The receipt of batch from the Sponsor is properly documented.

8. If batches of test and control substances are returned from distribution for redistribution, test and control substances are quarantined in a separate and identifiable area; the source of the return and the reason for the return are documented.

Every day of administration new flask with lyophilized product was allowed.

9. Batches of the test and control substances to be redistributed are reanalyzed to determine conformance to established specifications and redistributed only if all appropriate standards and specifications are met.

No.

10. Batches of returned test and control substances that do not conform to appropriate standards and specifications are not distributed without documentation of further appropriate investigations made and corrective actions taken.

No.

P. STUDY IMPLEMENTATION AND CONDUCT

1. A written detailed protocol including statistical methods is available and approved before the study initiation.

Yes.

2. The protocol contains the name of the sponsor, a descriptive title and statement of purpose; and,

Initial protocol contains descriptive title and statement of purpose.

3. The name of Study Director, as well as of scientists or professional persons, laboratory assistants and animal care personnel; and,

only the name of the Study Director.

4. The name and address of any contractors; and,

name and address of lab. testing.

5. Identification and stability of test and control substances; and,

Identification of the test substance.

6. Proposed dates for starting completion and submission of final reports; and,

No.

7. Specifications for the test systems including source (obtain name and address) and,

No.

8. Procedure for unique identification of test system if needed, the method for randomization, if any, and its justification; and,

No, but the dogs were caged individually.

9. Description of the diet used in the study as well as solvents, emulsified and/or other material (s) used to solubilize or suspend the test and control substance before mixing in the carrier.

No.

10. Route of administration of test and control substances and reason for its selection; and,

Yes.

11. Dosage levels (s), method and frequency of administration, and method to measure absorption; and,

Yes, except method to measure absorption.

12. Types and frequency of tests, analyses and measurements, and records to be maintained; and,

Yes.

13. Nonroutine procedures required to assure personnel health and safety.

No.

14. Changes or revisions to an approved protocol are documented, signed by the Study Director, dated and retained with the protocol.

Yes.

22. The age at sacrifice/death for each test and control test system; and,

Yes.

23. Gross pathology findings which are available to the pathologist examining the specimen microscopically, and

Yes.

24. Unforeseen circumstances that may affect the quality and integrity of the study are noted and documented; and,

Yes.

25. Unexpected health hazards to test systems are promptly reported to the appropriate supervisor and that corrective action taken is documented; and,

Yes corrective actions were taken if available and documented in the record.

26. The responses of test systems are documented; and,

Yes.

27. All required GLPs are followed; and

At the time when the study was conducted GLP were not available.

28. The study is carried out in a manner that provides for safety for laboratory personnel, and,

Yes.

29. All data, documentation, other information, protocols, specimens and final reports are transmitted to the archive.

Yes.

30. All data generated during the study are recorded, signed and dated in the required manner.

Not always. It was not officially requested at this period.

31. Test systems are monitored in conformity with the protocol.

Yes.

32. Animals moribund or found dead during a study are necropsied as specified in the protocol. Explain the operational procedures.

Yes Procedures of the action are documented in the record and final report.

O. REQUIRED DESCRIPTIVE OR QUANTITATIVE INFORMATION FOR COMPLETED ANIMAL STUDIES ONLY

a. Species being used in the study

Beagle dog.

b. Length of time that the animals were on study

30 days for quarantine; 30 days for treatment.

c. Number of animals loaded into the study:

1. on test substance : 12

2. on control : 6

d. Number of animals:

1. on test substance found dead : none

2. on test substance sacrificed : 12

3. on control found dead : none

4. on control sacrificed : 6

R. REPORTING OF NONCLINICAL LABORATORY STUDY RESULTS

1. The final report shall contain the name and address of the facility performing the study, and

Yes

2. dates on which study was initiated and completed; and,

Yes

3. the identity of the test and control substances, and

Yes

4. the name of the Study Director, and

Yes

5. A summary of data, and analysis of data, and a statement of the conclusions drawn from the analysis, and

Yes

6. reports of each individual scientist or other professional persons involved in the study, appropriately signed and dated and,

No

7. the location where all raw data and the final report are to be stored

Yes but not precisely the room and the rack.

8. The final report describes the objectives and procedures stated in the approved protocol, and

Yes

9. the data elements collected during the study, and

Yes

10. the statistical methods employed for analysing the data, and

Yes

11. the stability of the test and control substances under the conditions of administration, and

No see the report, the test substance was lyophilized and solution was prepared at the moment of the administration.

12. the methods used, and

Yes

13. the test system used, and

Yes

14. the dosage, dosage regimen, route of administration and duration; and,

Yes

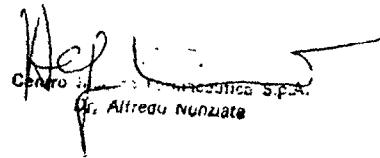
15. any unforeseen circumstances that may have affected the quality or integrity of the nonclinical laboratory study

Yes, if it is available.

Page 33

16. Amendments to the final report are clearly identified, justified, signed and dated.

No, the final report relates the correct execution of the study.

  
Centro di Ricerca e Sviluppo S.p.A.  
Dr. Alfredo Nunziata

**C R F - 026**

**TOXICOLOGICAL REPORT ON ESAFOSFINA PRODUCED BY  
BIOMEDICA FOSCAMA - ROME**

**ONE MONTH SUB-ACUTE TOXICITY IN DOG**

**BIOMEDICA FOSCAMA S.p.A.  
Chemical Pharmaceutical Industry  
Rome-Italy**

CRF - 026

TOXICOLOGICAL REPORT ON ESAFOSFINA

PRODUCED BY BIOMEDICA FOSCAMA - ROME

ONE MONTH SUB-ACUTE I.V. TOXICITY IN DOG

A) PREFACE

The Biomedica Foscama Co. of Rome requested a toxicological study of their product ESAFOSFINA<sup>R</sup> administered i.v. in Beagle dogs. The substance, a white lyophilized powder, was given to us in 5 g phials belonging to production lot n. 02 of January 22, 1976. This experiment is indicated in our files with the classification number CRF 026. A phial of the lyophilized substance marked BF CRF 026, together with its analysis certificate no. 10478 dated January 30, 1976 (a photocopy of which is attached), has also been saved in our archives.

The following documents are also filed in our archives with the same classification number :

- 1) Books and original clinical cards
- 2) Copy of the final report
- 3) Microscopic slides including :
  - a) blood smears for each animal
  - b) histological sections of every organ removed
- 4) Organs removed during autopsy in 10% neutral formaldehyde.

The material will be available for control for 5 years from the date of the present report.

B) EXPERIMENTAL PROTOCOL

18 five/seven month old Beagle dogs (9 males and 9 females) (body weight 6-9 Kg) were used for the experiment. The dogs, supplied by the Pellizzari Firm (Bergamo), had the prescribed vaccination certificates. They were kept under observation for 30 days prior to the experiment for possible vermination.

They were then randomly subdivided in 6 groups of three each (Group I - III - V for males and Group II - IV - VI for females). Each animal is identified by both individual and group number. The animals were kept in single cages in an air conditioned environment (18-20° C temperature and 50-55% relative humidity) and ate Mil Dog Pellet Food (Morini of S. Polo d'Enza) with water ad libitum.

The dose levels were selected on the basis of pharmacological information, human therapy dose and the maximum concentration solution :

200 mg/Kg per day i.v. to Groups I and II equal to 3 DTS

100 mg/Kg per day i.v. to Groups III and IV equal to 1.5 DTS

apyrogenic saline to Groups V and VI

2 ml/Kg of the substance was administered intravenously via vena sphenaea every day 6 days per week by slow phleboclysis (2 ml/minute). The controls were treated with 2 ml/kg of saline.

The animals' general conditions, behaviour and diet consumption were controlled daily. Body weight was measured every 5 days.

The solutions were prepared by dissolving 5 g of ESAFOSFINA<sup>R</sup> in 25 ml of bidistilled water which was brought to 50 ml for Dose I and to 100 ml for Dose II with sterile apyrogenic saline.

### LABORATORY TESTS

Biochemical and haematological tests (Table 1 and 2) were carried out before the experiment (zero time control) and after 1 month of treatment, so that there were two parameters of data for each animal that allow appraisal of the effects of treatment.

Before each sampling the animals were placed, one at a time, in a metabolic cage to collect urine on which the analysis listed in Table 3 were performed. After a careful autoptic screening, during autopsy, the organs listed in Table 4 were removed and weighed. The organs and tissues listed in Table 5 were fixed, embedded and examined histologically after normal staining procedures with Ematossina Eosina and Van Gieson.

# BIOMEDICA FOSCAMA

4

Industria Chimico-Farmaceutica s.p.a.  
00131 - Roma via Tiburtina Km. 15 - tel. 619 03.41

## ABORATORIO DI CONTROLLO CHIMICO

Controllo N. 0474

Materiale : FRUCTOSE-1,6-DIPHOSPHATE SODIC SALT LYOPHILIZED

[lotto o di preparazione] 07 Data di arrivo o preparazione 22/1/76

ornitore Quantità

### RISULTATI ANALITICI

humidity : 7,8%

sol. colour 10% : 300-100

Chlorides : inferiori 500 ppm

heavy metals : " 10 ppm

oxalic acid : absent

arsenic : lower than 5 ppm

pH sol. 5% : 5,75

Tot. phosphorus % : 1,3, 21 stq 14, 32 ss

inorganic% : 0,05 " 2,22 "

organic% : 11,16 " 12,10 "

Enzymatic titre : 78,5% stq 78,6% ss

### OSSERVAZIONI

APPROVED

ANALISTI

TEMPO

*D. Scattolon* FIRMA  
*Segato*

Data 31/1/76

Responsabile Laboratorio

*C. R. F. M. Scattolon* 07  
CONSORZIO INDUSTRIALE FARMACEUTICO S.p.A.

TABLE I  
Hematological tests performed after sacrifice of animal

The following haematological blood tests were performed :

Red blood cell count	(A)
White blood cell count	(A)
Haemoglobin determination	(A)
Haematocrit	(A)
Leucocyte formula	(M)
MCV	(A)

Tests marked (A) were performed with a SMA 4 Analyzer of Technicon Instruments Corp.

Ratios were calculated electronically.

Tests marked (M) were done manually according to classical procedures.

BIBLIOGRAPHY

1. Staining Procedures, The Williams and Wilkins Co., Baltimore, 1973
2. Methods in Toxicology, Paget G. E., Blackwell S.Pub., 338-371, 1970
3. The Blood Morphology of Laboratory Animals, Schermer S., F. A. Davis Co., Philadelphia, 1970

TABLE 2

BIOCHEMICAL BLOOD TESTS PERFORMED AFTER SACRIFICE

1. SGOT	(A)	2. SGPT	(A)
3. Albumin	(A)	4. Total protein	(A)
5. Alakli phosphatase	(A)	6. CO <sub>2</sub>	(A)
7. Urea	(A)	8. Glucose	(A)
9. Total bilirubin	(A)	10. Cholesterol	(A)
11. Inorganica phosphorous	(A)	12. LDH	(A)
13. Na	(C)	14. K <sup>+</sup>	(C)
15. Chlorides	(B)	16. Ca <sup>++</sup>	(B)

The tests marked (A) were performed simultaneously on a single blood sample with a SMA 12 Micro-Plus Analyzer, those marked (B) separately on a Technicon II Generaltion Analyzer.

BIBLIOGRAPHY

The following methods were used :

1. S. G. O. T.

Rush et All., Ame. Ass. Clin. Chem. Symposium, Buffalo 1970

2. S. G. .O.T.

Rush et All., Ame. Ass. Clin. Chem. Symposium, Buffalo 1970

Methods 1 and 2 are based on spectrophotometric readings of the change in optical density of NADH.

3. ALBUMIN

Boumas Watson, Clin. Chem. Acta 31, 87-96, 1971

Bromocresole green which lacks affinity to bilirubin and drugs is used.

4. TOTAL PROTEINS

Based on the Biureto reaction, it is the standard method for autoanalyzers.

5. ALKALI PHOSPHATASE

Morgensterns et Al., Clin. Chem. 11, 876, 1965

Based on the enzymatic hydrolysis of p-Nitrophenyl phosphate and on the quantity of freed p-Nitrophenol.

6. CO<sub>2</sub>

Based on the method of H. Hochstrasser, U.S. Pat. 3,572,1964 adapted to automation.

7. UREA

Marsh et All., Clin. Chem. II, 624, 1965

The urea reacts with diacetylmonoxima in the presence of thiosemicarbazide and ferric ions in an acid environment giving a colored compound.

8. GLUCOSE

Bittner McCleary, Ame. Jour. Clin. Path. 11, 423, 1963

9. TOTAL BILIRUBIN

Jendrassik and Grop, Bioch. Z. 297, 81, 1938

Modified by Gambino and Schriber.

Automation in Anal. Chemistry, Mediad Inc., N.Y., 1964

10. CHOLESTEROL

Huang, Anal. Chem. 33, 1405, 1961

11. INORGANIC PHOSPHOROUS

Robinson et Al., Ann. Clin. Bioch. 8, 168, 1971

12. LDH

Wacher et All., N. Eng. J. Med. 255, 449, 1956

Modified by Kessler et Al. in Advances in Automated Analyses 1, 6-7,  
1970

13.  $\text{Na}^+$  and  $\text{K}^+$

14. Flame spectrophotometer (Coleman)

15. CHLORIDES

Skeggs and Hochstrasser, Clin.Chem. 10, 918, 1964

16.  $\text{Ca}^{++}$

Wells R. Moorhead and Homer G. Biggs, Clin. Chem. 20/11, 14581460,  
1974

TABLE 3

URINE ANALYSES

- |             |                    |
|-------------|--------------------|
| 1. pH       | 5. Ketone bodies   |
| 2. Proteins | 6. Bilirubin       |
| 3. Glucose  | 7. Urobilinogenous |
| 4. Blood    | 8. Sediment        |

The determinations were carried out according to classical clinical laboratory procedures.

See for example : HANDBOOK OF CLINICAL LABORATORY DATA  
THE CHEMICAL RUBBER COMPANY  
CLEVELAND OHIO, 2nd EDITION 1968

TABLE 4

Organs that were removed and weighed after sacrifice and whose weights  
were used for statistical correlations :

Brain	Spleen
Pituitary gland	Kidneys
Thymus gland	Adrenal glands
Heart	Gonads
Liver	Uterus or prostate
Seminal vesicles	

TABLE 5

Organs and tissues which were removed for autopsy and fixed for inclusion  
and histopathological examination :

Adrenal glands	Gonads
Pituitary glands	Liver
Spleen	Intestine (3 levels)
Heart	Pancreas
Bladder	Stomach
Lung	Kidneys
Thymus-gland	Uterus or prostate
Brain	Bone marrow
Thyroid	Gall bladder
Esophagus	Trachea
Diaphragm	Mesenteric lymphatics
Epididymus	

C) EXPERIMENTAL SCHEDULE

- May, 12, 1976    9 males under diuresis
- May 13, 1976    Zero time blood samples are drawn from the 9 males  
and the 9 females are placed under diuresis.
- May 14, 1976    Zero time blood are drawn from the females.
- May 17, 1976    Treatment begins.
- June 18, 1976    All animals under diuresis
- June 21, 1976    Blood samples are drawn from the 18 dogs.
- June 22, 1976    Dogs 1 2 3 of Group I are sacrificed via i.v.injection of  
sodium pentothal and bleeding.
- June 23, 1976    Dogs 1 2 3 of Group II and 1 2 of Group III are sacrificed.
- June 24, 1976    Dog 3 of Group III and dogs 1 2 3 of Group IV and dog 1 of  
Group V are sacrificed.
- June 25, 1976    Dogs 2 3 of Group I and dogs 1 2 3 of Group VI are  
sacrificed.

D) RESULTS

Statistical Evaluations

The one way variance analysis test for groups (1) was applied to the biochemical, blood and autoptic data, and the uniformity of the variance was checked out with Bartlett's test.

The calculations, performed on a Litton Monroe 1860 computer, and reported in the table, reflect single values, with averages, +/- S. E. and the confidence limits for each group.

The variance analysis table reports the averages for the groups, +/- S.E., Fisher's F and the significance level. For significant Fisher's F, the treated group which is statistically different compared to the control is also indicated.

Diet consumption is reported in the tables as the group's average value over time.

The animals' growth curve values are processed statistically according to GRAY and ADDIS where the logarithm of the average group weight is an inverse function of time; a linear function is thus obtained that enables statistical comparison between groups.

- 1) W. G. Snedecor, G. W. Cochran, Statistical Methods, VI ed., 258,  
THE IOWA UNIVERSITY PRESS, 1967

**D) RESULTS**

**C - 1) General Behaviour**

No changes in behaviour or general conditions were observed in the dogs treated with ESAFOSFINA<sup>R</sup> for one month.

None suffered from diarrhea, vomit; there were no changes in the respiratory apparatus, the cardiovascular system or reflects on the C.N.S.

**C - 2) Growth and diet consumption**

Graph 1 and the clinical reports for each animal show that growth, although limited due to the duration of the experiment, was normal in all groups and at all doses. This is confirmed by the diet consumption trend in the male group on the highest dose which was the highest. The females' diet consumption pattern is similar in both treated and controls.

**C - 3) Autoptic results**

Direct observation of the animals during autopsy did not reveal lesions that could be linked to the sub-acute treatment with ESAFOSFINA<sup>R</sup>. The following lesions were found in four animals:

- Dog 1, Group I : enlarged right kidney with small hollows and a variegated cutting surface
- Dog 1 and 2, Group III : enlarged lung volume with rough surface section
- Dog 1, Group V : underdeveloped testicles for age group.

No pathological conditions were found in any of these dogs or in any other organ. The lesions found should be considered incidental and independent of treatment.

C - 3 - a) Absolute weight of organs

All values are normal. The parameters of treated and control animals do not differ significantly.

C - 3 - b) Relative weight of organs

Significantly higher values were found in the weight of the liver of the treated animals, for both sexes. In the females, moreover, the weight of the ovaries and the thymus gland were significantly different. The liver's higher weight in the case of the males appears to be related to the dose, whereas for the other cases this correlation does not exist.

C - 4) Haematological tests

Average haematological values and the haematological values for each animal at zero time were normal proving their excellent initial clinical conditions. At the end of the experiment, there are significant variances for HCT and haemoglobin: lower in the treated males compared to controls and females. The females show a significant decrease of red blood cells linked to a rise in the MCV.

The haematological parameters of the individual animals range within normal values for 5-7 month old Beagle dogs. The statistical variances do not have biological significance but are incidental.

C - 5) Biochemical analyses

The average biochemical and zero time values for each animal are normal and show the homogeneity of the animals and their initially excellent clinical conditions. After one month of treatment, the statistically significant values are distributed as follows :

Inorganic phosphorous : significantly higher than controls  
in both males and females

Lactic dehydrogenase : significantly higher than controls  
in both males and females

$\text{Na}^+$  and  $\text{K}^+$ : lower than controls in males

The biochemical parameters of the individual animals range within normal values for Beagle dogs. Individual variations of biochemical and hematological alterations are linked to noxae of spontaneous pathology of the animal species selected, and they were studied in the autopic and histological examinations performed.

HISTOLOGICAL REPORTTIME = 1 MONTHDOGS "BEAGLE"

1 month after the beginning of the treatment, a histological control is performed on the organs of 18 "Beagle" dogs under going daily intravenous administration of "ESAFOSFINA" in order to emphasize eventual toxic effects due to this drug. The fragments of organs are fixed in 10% neutral formalin and preserved in paraffin.

The strips on the slides are subjected to the following colouring:  
hematoxylin-eosin and Van Gieson.

Histological data relating to each group and single animal  
are hereinafter set out:

- Group I - n. 1 - intertubular lymphocytic infiltrations  
of kidney:
- " II - n. 2 } - NN  
3 }  
" III - 1 - pulmonal histiocytic granuloma;  
2 - pulmonal chronic-reactive aspecific  
histiocytic granuloma;  
3 - NN
- " IV - n. 1 } -  
2 } - NN  
3 } -
- " V - n. 1 - testicle atrophy, hypophysis hyaline  
cystis:  
2 - NN  
3 - NN
- " VI - n. 1 } -  
2 } - NN  
3 } -

## TOXICOLOGICAL DEPARTMENT

C.R.F.

CONCLUSIONS

Microscopic examination of the organs of the dogs treated for 1 month with ESAFOSFINA<sup>R</sup> has shown the presence of two types of lesions: neoplastic in the lungs and inflammatory in the kidneys and adrenal glands.

Such alterations, which were found only in the males, are distributed in a way that does not indicate a correlation with the drug's doses. They may therefore be considered incidental pathological events unrelated to treatment.

Histologically, there are no signs of irritation or toxicity in the various organs and tissues. The product, therefore, lacks toxic effects.

Pomezia, October 7, 1976

F) CONCLUSIONS AND COMMENTS

From the examination of the data contained in this report, it is possible to state that, in our experimental conditions and dose levels, the substance tested, ESAFOSFINA<sup>R</sup> produced by BIOMEDICA FOSCAMA of Rome, does not show toxic effects.

The doses chosen were higher than would normally be used in clinical therapy :

Group I - 200 mg/Kg i.v. = 2.60 DTS

Group II - 100 mg/Kg i.v. = 1.30 DTS

Statistically significant biochemical and haematological variations were found, which nevertheless are restricted within the normal range for the species. The statistical variations found depend on the variations of one individual in a group and do not represent the tendency of that group. Probably from a biochemical viewpoint, such variations, which are normally found in the species, arise out of the individual animal's capacity to reestablish the homeostatic equilibrium that had been acutely altered by the repeated administration of non physiological quantities of liquids and salts.

From the dog's individual capacity to counteract the exogenous action derive the small variations of the individual biochemical composition.

Hence, in conclusion ESAFOSFINA is a product that is well tolerated by animal organisms, also in case of repeated administration, and that is free of toxic effects.

## ICL.R.F. TOXICOLOGIC DEPARTMENT

1 MONTH

30

BIOCHEMICAL VALUES ANALYSIS OF VARIANCE EXPERIMENT n 026 SEX M STRAIN Beagle

GROUP I GROUP III GROUP V F Signif.

CO <sub>2</sub>	meq/l	21.667 ± 0.8819	21.000 ± 1.0000	21.667 ± 1.2019	0.13	N.S.
Prot.Tot.	g%	8.100 ± 0.1155	8.233 ± 0.2728	8.067 ± 0.4256	0.08	N.S.
Albumine	g%	4.067 ± 0.0882	4.433 ± 0.1202	4.300 ± 0.4041	0.55	N.S.
Inorg. P.	mg%	9.833 ± 0.0882	8.400 ± 0.3000	8.367 ± 0.5364	5.45	0.05
Cholest.	mg%	140.000 ± 10.0000	141.667 ± 18.5592	173.333 ± 19.2209	1.30	N.S.
Glucos <sup>e</sup>	mg%	111.667 ± 3.3333	115.000 ± 5.7735	118.333 ± 8.8192	0.27	N.S.
BUN	mg%	16.267 ± 1.2252	20.933 ± 3.1593	15.063 ± 1.187	2.23	N.S.
Bilirub.T.	mg%	0.433 ± 0.0667	0.533 ± 0.0882	0.483 ± 0.0726	0.42	N.S.
Alk.phosph.,mU/ml	140.000 ± 20.0000	143.333 ± 9.2796	246.667 ± 63.0035	2.47	N.S.	
LDH	mmU/ml	0.425 ± 0.0875	0.278 ± 0.0044	0.182 ± 0.0303	5.23	0.05 2
SGPT	mU/m	31.667 ± 4.4096	35.000 ± 5.7735	53.333 ± 10.9291	2.37	N.S.
SGOT	mU/ml	75.000 ± 12.5731	66.667 ± 1.6667	55.000 ± 5.0000	1.62	N.S.
Cl ion	meq/l	136.667 ± 2.7285	135.667 ± 2.7285	147.667 ± 8.0898	1.65	N.S.
Na ion	meq/l	126.667 ± 2.7285	152.333 ± 3.5277	165.333 ± 7.3106	15.83	0.01 1
K ion	meq/l	4.500 ± 0.1000	4.867 ± 0.1453	5.500 ± 0.2517	8.12	0.05 1
Ca <sup>++</sup>	mg%	12.767 ± 0.3930	13.700 ± 0.4000	13.133 ± 0.4096	1.37	N.S.

DATA : 27/9/76

FIRMA

CONSORZIO AEREA FARMAEUTICA SPA  
Aeritalia - Farma

## C.R.F. TOXICOLOGIC DEPARTMENT

1 MONTH

31

BIOCHEMICAL VALUES	ANALYSIS OF VARIANCE			EXPERIMENT	n	O26	SEX	F	STRAIN	Beagle
	GROUP	II	GROUP	IV	GROUP	VI				

CO <sub>2</sub>	meq/l	20.333	$\pm$	0.8819	21.000	$\pm$	0.5774	17.333	$\pm$	2.1858	1.94	N.S.
Prot.Tot.	g%	8.067	$\pm$	0.1856	7.567	$\pm$	0.1764	7.033	$\pm$	0.7055	1.42	N.S.
Albumine	g%	4.000	$\pm$	0.1155	3.800	$\pm$	0.1528	3.667	$\pm$	0.1856	1.18	N.S.
Inorg. P.	mg%	9.600	$\pm$	0.5508	7.600	$\pm$	0.5132	6.367	$\pm$	0.2667	12.52	0.01
Cholest.	mg% 100.000	$\pm$ 10.0000	123.333	$\pm$ 10.1379	126.667	$\pm$ 14.2400	0.081	N.S.				
Glucose	mg% 106.667	$\pm$ 1.668	110.000	$\pm$ 5.0000	93.333	$\pm$ 4.4096	4.98	N.S.	1			
BUN	mg%	17.600	$\pm$	2.7301	15.033	$\pm$	0.2186	17.333	$\pm$	1.8586	0.54	N.S.
Bilirub.T.	mg%	0.567	$\pm$	0.0333	0.500	$\pm$	0.0577	0.663	$\pm$	0.0333	3.80	N.S.
Alk.phosph. mU/ml	113.333	$\pm$ 15.8990	105.000	$\pm$ 0.0000	120.000	$\pm$ 10.4073	0.46	N.S.				
LDH	mmU/ml	0.287	$\pm$	0.0367	0.230	$\pm$	0.0104	0.267	$\pm$	0.0467	0.68	N.S.
SGPT	mU/ml	45.000	$\pm$	2.8868	38.333	$\pm$ 10.1379	40.000	$\pm$ 2.8868	0.30	N.S.		
SGOT	mU/ml	70.000	$\pm$	5.7735	63.333	$\pm$ 4.4096	60.000	$\pm$ 5.0000	1.00	N.S.		
Na ion	meq/l	137.667	$\pm$	8.1104	142.333	$\pm$ 1.7638	134.000	$\pm$ 4.6188	0.58	N.S.		
Na ion	meq/l	160.667	$\pm$	6.3596	168.000	$\pm$ 3.6056	168.333	$\pm$ 3.3830	0.86	N.S.		
K ion	meq/l	5.600	$\pm$	0.4041	5.467	$\pm$ 0.2028	5.500	$\pm$ 0.2082	0.05	N.S.		
Ca <sup>++</sup>	mg%	12.933	$\pm$	0.8090	13.700	$\pm$ 0.2000	12.067	$\pm$ 0.2333	2.67	N.S.R. F. 2		

DATA: 27/9/76

FIRMA

CONSORZIO RICERCHE FARMACEUTICA S.P.A.  
di Alfredo Nunziata



IRCP  
Istituto di Ricerca e Controllo per la Farmacologia S.p.A.

1 MONTH

32

GROUP I SEX M STRAIN Beagle EXPERIMENT 026 TREATMENT 200mg/Kg in 2ml/Kg ev BIOCHEMICAL CARD

		1.	2.	3.	M.	L.F.	<u>E.S.</u>
CO <sub>2</sub>	meg/l	22.00	20.00	23.00	21.67	25.46	17.87
Prot.Tot.	g%	78.10	8.30	7.90	8.10	7.60	0.115
Albumine	g%	4.20	4.10	3.90	4.0	4.45	3.69
Inorg. P.	mg%	10.00	9.70	9.80	9.83	10.21	9.45
Cholest.	mg%	130.00	160.00	130.00	140.00	183.03	96.97
Glucose	mg%	115.00	105.00	115.00	111.67	126.01	97.32
BUN	mg%	13.90	16.90	18.00	16.27	21.54	11.00
Bilirub.T.	mg%	0.30	0.50	0.50	0.43	0.72	0.15
Alk.phosph	mU/ml	160.00	160.00	100.00	140.00	226.05	53.95
LDH	mmU/ml	0.60	0.34	0.34	0.43	0.80	0.05
SGPT	mU/ml	40.00	30.00	25.00	31.67	50.64	12.69
SGOT	mU/ml	100.00	60.00	65.00	75.00	129.14	20.86
Cl ion	meq/l	135.00	133.00	142.00	136.67	148.41	124.93
Na ion	meq/l	123.00	125.00	132.00	126.67	138.41	134.93
K ion	meq/l	4.70	4.40	4.40	4.50	4.93	4.07
Ca <sup>++</sup>	mg%	12.00	13.00	13.30	12.77	14.46	11.08

DATA: 27/9/76

FIRMA: *R. Nunziata*  
IRCP - ISTITUTO DI RICERCA FARMACEUTICA S.p.A.  
Mr. Alfredo Nunziata



**CRF**  
consorzio ricerca  
farmaceutica spa

1 MONTH

39

GROUP II SEX F STRAIN Beagle EXPERIMENT 026 TREATMENT 100mg/Kg i.v./ml/Kg ev. BIOCHEMICAL CARD

		1.	2.	3.	M.	L.F.	<u>E.S.</u>
CO <sub>2</sub>	meq/l	20.00	19.00	22.00	20.33	24.13	16.54
Prot.Tot.	g%	7.70	8.20	8.30	8.07	8.87	7.27
Albumine	g%	3.80	4.20	4.00	4.00	4.50	3.50
Inorg. P.	mg%	9.70	8.60	10.50	9.60	11.97	7.23
Cholest.	mg%	140.00	110.00	110.00	120.00	163.03	76.97
Glucose	mg%	105.00	110.00	105.00	106.67	113.84	99.50
BUN	mg%	14.20	15.60	23.00	17.60	29.35	5.85
Bilirub.T.	mg%	0.50	0.60	0.60	0.57	0.71	0.42
Alk.phosph:mU/ml	mU/ml	100.00	95.00	145.00	113.33	184.74	44.92
LDH	mmU/ml	0.25	0.36	0.25	0.29	0.44	0.13
SGPT	mU/ml	40.00	45.00	50.00	45.00	57.42	32.58
SGOT	mU/ml	60.00	70.00	80.00	70.00	98.84	45.16
Cl ion	meq/l	139.00	123.00	151.00	137.6	172.56	102.77
Na ion	meq/l	150.00	172.00	160.00	160.67	188.03	133.30
K ion	meq/l	5.10	6.40	5.30	5.60	7.34	3.86
Ca <sup>++</sup>	mg%	13.00	11.50	14.30	12.93	16.41	9.45

DATA: 27/9/76

FIRMA:

C. R. F.  
CONSORZIO RICERCA FARMACEUTICA S.p.A.  
Dr. Alfredo Munizata



**CRP**  
consorzio ricerca  
farmaceutica s.p.a.

1 MONTH

34

GROUP III SIX M STRAIN Beagle EXPERIMENT 026 TREATMENT 100mg/Kg in 2ml/Kg ev BIOCHEMICAL CARD

		1.	2.	3.	M.	L.F.	<u>±E.S.</u>
CO <sub>2</sub>	meq/l	23.00	20.00	20.00	21.00	25.30	16.70
Prot. Tot.	g%	8.60	7.70	8.40	8.23	9.41	7.06
Albumin	g%	4.60	4.20	4.50	4.43	4.95	3.92
Inorg. P.	mg%	8.10	9.00	8.10	8.40	9.69	7.11
Cholest.	mg%	105.00	165.00	155.00	141.67	221.52	61.81
Glucose	mg%	105.00	125.00	115.00	115.00	139.84	90.16
BUN	mg%	26.10	21.50	15.20	20.93	34.53	7.34
Bilirub.T.	mg%	0.50	0.40	0.70	0.53	0.91	0.15
Alk.phosph	μU/ml	125.00	150.00	155.00	143.33	183.26	103.41
LDH	mmU/ml	0.27	0.28	0.29	0.28	0.30	0.26
SGPT	μU/ml	35.00	45.00	25.00	35.00	59.84	10.16
SGOT	μU/ml	65.00	65.00	70.00	66.67	73.84	59.50
Cl ion	meq/l	141.00	134.00	132.00	135.67	147.41	123.93
Na ion	meq/l	147.00	151.00	159.00	152.33	167.51	137.15
K ion	meq/l	4.60	4.90	5.10	4.87	5.49	4.24
Ca <sup>++</sup>	mg%	14.50	13.30	13.30	13.70	15.42	11.98

DATA: 27/9/76

FIRMA: *[Signature]*  
CONSORZIO RICERCA FARMACEUTICA S.p.A.  
Dr. Alfredo Vassalli

**CONSORZIO RICERCA  
FARMACEUTICA S.p.A.**

1 MONTH

**35**

GROUP IV SEX F STRAIN Beagle EXPERIMENT 026 TREATMENT 100mg/Kg in 2ml/Kg ev. BIOCHEMICAL CARD

		1.	2.	3.	M.	L.F.	<u>E.S.</u>
2	meq/l	20.00	22.00	21.00	21.00	23.48	18.52
ot.Tot.	g%	7.90	7.30	7.50	7.57	8.33	6.81
bumine	g%	4.00	3.50	3.90	3.80	4.46	3.14
org. P.	mg%	8.60	6.90	7.30	7.60	9.81	5.39
colest.	mg%	140.00	105.00	125.00	123.33	166.95	79.71
lucose	mg%	115.00	100.00	115.00	110.00	131.51	88.49
JN	mg%	14.60	15.20	15.30	15.03	15.97	14.09
ilirub.T.	mg%	0.40	0.60	0.50	0.50	0.75	0.25
uk. phosphmU/ml	105.00	105.00	105.00	105.00	105.00	105.00	0.000
DH	mmU/ml	0.23	0.22	0.25	0.23	0.27	0.19
GPT	mU/ml	20.00	55.00	40.00	38.33	81.95	-5.29
GOT	mU/ml	70.00	65.00	55.00	63.33	82.31	44.36
Ca ion.	meq/l	145.00	143.00	139.00	142.33	149.92	134.74
Ka ion.	meq/l	166.00	175.00	163.00	168.00	183.51	152.49
Na ion	meq/l	5.80	5.10	5.50	5.47	6.34	4.59
Ca++	mg%	13.90	13.30	13.90	13.70	14.56	12.84

DATA: 27/9/76

FIRMA:

C. R. F.  
CONSORZIO RICERCHE FARMACEUTICHE S.p.A.  
Dr. Alfredo Nunziata



**CRF**  
Consorzio ricerca  
farmaceutica s.p.a.

36

1 MON71

GROUP V SIX M STRAIN Beagle EXPERIMENT 026 TREATMENT PHYSOL SOL. IN 2ml/Kg ev BIOCHEMICAL CARB

		1.	2.	3.	M.	L.F.	E.S.
CO <sub>2</sub>	meq/l	20.00	21.00	24.00	21.67	26.84	16.50
Prot.Tot.	g%	7.50	7.80	8.90	8.07	9.90	6.24
Albumine	g%	4.00	3.80	5.10	4.30	6.04	2.56
Inorg. P:	mg%	7.60	7.10	9.40	8.37	10.67	6.06
Cholest.	mg%	165.00	145.00	210.00	173.33	256.04	90.63
Glucose	mg%	115.00	105.00	135.00	118.33	156.28	80.39
BUN	mg%	16.30	12.70	16.20	15.07	20.16	9.97
Bilirub.T.	mg%	0.60	0.50	0.35	0.48	0.80	0.17
Alk.phosphU	mU/ml	150.00	225.00	365.00	246.67	517.75	-24.42
LDH	mmU/ml	0.18	0.13	0.24	0.18	0.31	0.05
SGPT	mU/ml	75.00	45.00	40.00	53.33	100.36	6.31
SGOT	mU/ml	50.00	50.00	65.00	55.00	76.51	33.49
Ca ion	meq/l	147.00	134.00	162.00	147.67	124.47	112.86
Na ion	meq/l	151.00	170.00	175.00	165.33	196.79	133.88
K ion	meq/l	5.20	5.30	6.00	5.50	6.58	4.42
Ca <sup>++</sup>	mg%	13.90	13.00	12.50	13.13	14.90	11.37

DATA: 27/9/76

FIRMA: UNISOLZIO RICERCA ARMAMENTA S.p.A.

C. R. F.  
CIRURGICO RICERCA FARMAZENTRA S.p.A.  
Dr. Alfredo Nunziata



**CRF**  
consorzio ricerca  
farmaceutica s.p.a.

### 1 MONTH

37

GROUP	VI	SFX . F	STRAIN	Beagle	EXPERIMENT	O26	TREATMENT	PHYSIOL.	SOL in 2ml/Kg ev	BIOCHEMICAL CARD
			1.	2.	3.	M.	L.F.		<u>±E.S.</u>	
CO <sub>2</sub>	meg/l	13.00	19.00	20.00	17.33	26.74	7.93	2.186		
Prot.Tot.	g%	5.70	7.30	8.10	7.03	10.07	4.00	0.706		
Albumin.e	g%	3.30	3.90	3.80	3.67	4.47	2.87	0.186		
Inorg. P.	mg%	6.10	6.10	6.90	6.37	7.51	5.22	0.267		
Cholest.	mg%	110.00	155.00	115.00	126.67	187.94	65.40	14.240		
Glucose	mg%	85.00	95.00	100.00	93.33	112.31	74.36	4.410		
BUN	mg%	18.10	20.10	13.80	17.33	25.33	9.34	1.859		
Bilirub.T.	mg%	0.70	0.70	0.60	0.67	0.81	0.52	0.033		
Alk.phosph/mU/ml	105.00	140.00	115.00	120.00	164.78	75.22	10.40			
LDH	mmU/ml	0.22	0.36	0.22	0.27	0.47	0.07	0.047		
SGPT	mU/ml	40.00	45.00	35.00	40.00	52.42	27.58	2.887		
SGOT	mU/ml	50.00	65.00	65.00	60.00	81.51	38.49	5.000		
Cl ion	meq/l	142.00	134.00	126.00	134.00	153.87	114.13	4.619		
Na ion	meq/l	175.00	164.00	166.00	168.33	182.89	153.78	3.383		
K ion	meq/l	5.10	5.80	5.60	5.50	6.40	4.60	0.208		
Ca <sup>++</sup>	mg%	11.70	12.50	12.00	12.07	13.07	11.06	0.233		

DATA: 27/9/76

FIRMA: Dr. Alfredo Nunziata

20

C.R.F.  
TOXICOLOGIC  
DEPARTMENT

TIME = 1 MONTH

38

					EXPERIMENT	n 026	SEX	M	STRAIN	Beagle
	GROUP I	GROUP III	GROUP V		F		Signi.	+		
Hct %	45.828 ± 0.8819	48.333 ± 0.8819	49.667 ± 0.6667		7.38		0.05	1		
LeuK. x 1000	6.800 ± 0.4000	8.267 ± 1.3920	7.700 ± 0.3606		0.73		N.S.			
Hb g% ml	10.733 ± 1.2347	14.333 ± 0.5333	14.733 ± 0.7513		6.13		0.05			
Erythrocy. x million	7.200 ± 0.2309	6.933 ± 0.0667	7.533 ± 0.5457		0.76		N.S.			
MCV	63.167 ± 3.2503	69.667 ± 0.8838	66.600 ± 4.8125		0.91		N.S.			
F Neutr.	41.333 ± 7.6884	45.333 ± 3.7118	60.000 ± 6.4291		2.53		N.S.			
O										
R Lymph.	56.000 ± 7.2111	46.000 ± 3.0551	34.667 ± 4.8074		4.04		N.S.			
M										
U Mon.	0.000 ± 0.0000	0.000 ± 0.0000	0.000 ± 0.0000		0.00		N.S.			
L										
A Eosin.	2.667 ± 0.6667	8.667 ± 3.3333	5.333 ± 1.7638		1.84		N.S.			
Bas.	0.000 ± 0.0000	0.000 ± 0.0000	0.000 ± 0.0000		0.00		N.S.			
Plat. x1.000	525.000 ± 13.5782	370.000 ± 40.1040	375.000 ± 8.6603		1.59		N.S.			
Ret.mmc	0.533 ± 0.1202	0.300 ± 0.1000	0.333 ± 0.0882		1.48		N.S.			
T.Prot .sec	9.833 ± 1.5899	8.500 ± 0.0000	9.333 ± 0.3333		0.51		N.S.			

Data : 27/9/76

Firma

C. R. F.  
INSTITUTO DE INVESTIGACIONES FARMACEUTICAS S.A.  
Dr. Alfredo Nunziata



Centro di Ricerca  
Farmaceutica

TIME = 1 MONTH

39

C.R.F. TOXICOLOGIC DEPARTMENT  
HIMATOLOGIC VALUES ANALYSIS OF VARIANCE EXPERIMENT n026 SEX F STRAIN Beagle

	GROUP II	GROUP IV	GROUP VI	GROUP	F	Signf.
Hct %	46.000 ± 1.0000	47.667 ± 1.7638	51.000 ± 0.5774	4.37	N.S.	1
Leuk. x 1000	3.200 ± 0.6110	8.000 ± 1.1547	7.767 ± 0.3180	0.28	N.S.	
Hb g% ml	11.533 ± 1.1392	12.600 ± 1.5875	15.133 ± 0.5925	2.46	N.S.	1
Erythrocy. x millions	6.133 ± 0.1333	6.933 ± 0.3528	7.667 ± 0.1764	10.17	0.01	1
MCV	76.333 ± 1.3333	68.833 ± 0.9333	66.933 ± 2.2586	9.56	0.01	1
F Neutr.	54.667 ± 12.6667	59.000 ± 8.5440	67.667 ± 1.4530	0.55	N.S.	
O						
R Lymph.	37.333 ± 11.3333	36.000 ± 8.029	28.333 ± 4.4096	0.33	N.S.	
M						
U Mon.	0.000 ± 0.0000	2.000 ± 2.0000	0.000 ± 0.0000	1.00	N.S.	
L						
A Eosin.	8.000 ± 3.0551	3.000 ± 0.5774	4.000 ± 3.0551	1.10	N.S.	
Bas.	0.000 ± 0.0000	0.000 ± 0.0000	0.000 ± 0.0000	0.00	N.S.	
Plat. x1.000	348.333 ± 96.1480	460.000 ± 96.7385	300.000 ± 17.5594	1.06	N.S.	
RET.mm	0.467 ± 0.0667	0.667 ± 0.2333	0.500 ± 0.1000	0.50	N.S.	
T.Prot .sec	9.333 ± 0.4410	9.333 ± 0.1667	9.333 ± 0.4410	0.00	N.S.	

Data: 27/9/76

Firma

C. R. F.  
CENTRO DI RICERCA FARMACEUTICA S.p.A.  
Dr. Alfredo Nunziata



CRF  
consorzio ricerci  
farmaceutici

TIME: 1 MONTH

40

GROUP I SEX M STRAIN Beagle EXPERIMENT 026 TREATMENT 200mg/Kg 2 ml/Kg ev HEMATOLOGIC CARD

	1.	2.	3.	M.	L.F.	<u>E.S.</u>
HCT %	44.00	47.00	45.00	45.33	49.13	41.54

Leuk. $\times 1.000$  37.20 7.20 6.00 6.80 8.52 5.08 0.400

Hb g/ml 9.40 13.20 9.60 10.73 16.05 5.42 1.235

Erythrocytes millions 7.60 6.80 7.20 7.20 8.19 6.21 0.231

MCV 57.90 69.10 62.50 63.17 77.15 49.18 3.250

FORMULA

Neutr. 30.00 38.00 56.00 41.33 74.41 8.25 7.688

Lymph. 66.00 60.00 42.00 56.00 87.03 24.97 7.211

Mon. 0.00 0.00 0.00 0.00 0.00 0.00 0.000

Eosin. 4.00 2.00 2.00 2.67 5.54 -0.20 0.667

Basof. 0.00 0.00 0.00 0.00 0.00 0.00 0.000

Plat.  $\times 1.000$  705.00 555.00 315.00 525.00 1013.69 36.31 113.578

Ret. mm 0.60 0.30 0.70 0.53 1.05 0.02 0.120

T.Prot. sec 13.00 7.50 8.00 9.83 16.67 2.99 1.590

C. R. F.  
MONSANTO PHARMA INDUSTRIE S.p.A.  
FIRMA: *R. P. D'Adda*

DATA: 27/9/76



CNR  
consorzio ricerca  
industria e p.d.

TIME = 1 MONTH

41

GROUP	II	SIX	F	STRAIN	Beagle	EXPERIMENT	026	TREATMENT	200mg/Kg 2 ml/Kg ev	HEMATOLOGIC CARD
<hr/>										
	1.	2.	3.	M.		L.F.		<u>±E.S.</u>		
HCT %	45.00	38.00	45.00	46.00	50.30	41.70		1.000		
Leuk. x1.000	6.00	8.00	7.60	7.20	9.83	4.57		0.611		
Hb g/ml	10.60	13.80	10.20	11.53	16.43	6.63		1.139		
Erythrocy. x millions	6.00	6.40	6.00	6.13	6.71	5.56		0.133		
MCV	75.00	79.00	75.00	76.33	82.07	70.60		1.333		
<hr/>										
FORMULA										
Neutr.	62.00	30.00	72.00	54.67	109.17	0.17		12.68		
Lymph.	26.00	60.00	26.00	37.33	86.10	-11.43		11.333		
Mon.	0.00	0.00	0.00	0.00	0.00	0.00		0.000		
Eosin.	12.00	10.00	2.00	8.00	21.14	-5.14		3.055		
Basof.	0.00	0.00	0.00	0.00	0.00	0.00		0.000		
Plat. x1.000	535.00	215.00	295.00	348.33	762.03	-65.36		96.148		
Ret. mmc	0.60	0.40	0.40	0.47	0.75	0.18		0.067		
T.Prot. sec	10.00	9.50	8.50	9.33	11.23	7.44		0.441		

DATA: 27/9/76

C. R. F.  
FIRMA: *Alfredo Munizata*  
Dr. Alfredo Munizata



**CRF**  
consorzio ricerca  
farmaceutica s.p.a.

TIME = 1 MONTH

42

GROUP	III	SEX	M	STRAIN	Beagle	EXPERIMENT	O26	TREATMENT	IC0mg/Kg 2 ml/Kg ev	HEMATOLOGIC CARD
								L.F.	+E.S.	
HCT %		1.	2.	3.	M.					
		48.00	47.00	50.00	48.33	52.13	44.54	0.882		
Leuk. x1.000		10.80	6.00	8.00	8.27	14.26	2.28	1.392		
Hb g/ml		13.80	13.80	15.40	14.33	16.63	12.04	0.533		
Erythrocy. x millions		7.00	6.80	7.00	6.93	7.22	6.65	0.067		
MCV		68.50	69.10	71.40	69.67	73.47	65.86	0.884		
FORMULA										
Neutr.		38.00	46.00	50.00	45.33	61.30	29.36	3.712		
Lymph.		50.00	40.00	48.00	46.00	59.14	32.86	3.055		
Mon.		0.00	0.00	0.00	0.00	0.00	0.00	0.000		
Eosin.		12.00	12.00	2.00	8.67	23.01	-5.68	3.333		
Basof.		0.00	0.00	0.00	0.00	0.00	0.00	0.000		
Plat. x1.000		450.00	335.00	325.00	370.00	542.56	197.44	40.104		
-Ret. mmc		0.50	0.20	0.20	0.30	0.73	-0.13	0.100		
T.Prot . sec		8.50	8.50	8.50	8.50	8.50	8.50	0.000		

DATA: 27/9/76

**FIRMA:**

P. R. F.  
CONSORZIO DI CERCA FARMACEUTICA S.P.A.  
Dr. Alfredo Nunziata



**CRF**  
consorzio ricerca  
farmaceutica s.p.a.

TIME = 1 MONTH

43

GROUP IV SEX F STRAIN Beagle EXPERIMENT 026 TREATMENT 100mg/Kg 2 ml/Kg ev HEMATOLOGIC CARD

	1.	2.	3.	M.	L.F.	<u>E.S.</u>	
HCT %	45.00	47.00	51.00	47.67	55.26	40.0	1.764
Leuk. x1.000	6.00	10.00	8.00	8.00	12.97	3.03	1.155
Hb g/ml	10.20	12.00	15.60	12.60	19.43	5.77	1.587
Erythrocy. x millions	6.40	6.80	7.60	6.93	8.45	5.42	0.353
MCV	70.30	69.10	67.10	67.83	72.85	64.82	0.933
FORMULA							
Neutr.	52.00	76.00	49.00	59.00	95.76	22.24	8.544
Lymph.	46.00	20.00	42.00	36.00	70.78	1.22	8.0
Mon.	0.00	0.00	6.00	2.00	10.61	-6.61	2.000
Eosin.	2.00	4.00	3.00	3.00	5.48	0.52	0.57
Basof.	0.00	0.00	0.00	0.00	0.00	0.00	0.000
Plat. x1.000	455.00	630.00	295.00	460.00	876.24	43.76	96.738
Ret. mmc	0.90	0.20	0.90	0.67	1.67	-0.34	0.233
T.Prot . sec	9.00	9.50	9.50	9.33	10.05	8.62	0.167

DATA: 27/9/76

FIRMA: *C. R. F.*  
CONSORZIO RICERCA FARMACEUTICA S.p.A.  
Dr. Alfredo Nunziata



C.R.F.  
consorzio ricerca  
farmaceutica s.p.a.

TIME = 1 MONTH

44

GROUP	V	SEX	M	STRAIN	BEAGLE	EXPERIMENT	026	TREATMENT	CONTROLS	PHYSIOL.	SOL.	HEMATOLOGIC CARD.
<hr/>												
								1.	2.	3.	M.	L.F.
HCT %				51.00	49.00	49.00		49.67	52.54	46.80	0.667	
Leuk. x1.000				7.50	7.20	8.40		7.70	9.25	6.15	0.361	
Hb g/ml				16.00	14.80	13.40		14.73	17.97	11.50	0.751	
Erythroc. x millions				7.20	6.80	8.60		7.53	9.88	5.19	0.546	
MCV				70.80	72.00	57.00		66.60	87.31	45.89	4.812	
<hr/>												
FORMULA												
Neutr.				70.00	62.00	48.00		60.00	87.66	32.34	6.429	
Lymph.				28.00	32.00	44.00		34.67	55.35	13.98	4.80	
Mon.				0.00	0.00	0.00		0.00	0.00	0.00	0.000	
Eosin.				2.00	6.00	8.00		5.33	12.92	-2.26	1.764	
Basof.				0.00	0.00	0.00		0.00	0.00	0.00	0.000	
Plat. x1.000				360.00	390.00	375.00		375.00	412.26	337.74	8.660	
R&t. mmrc				0.30	0.20	0.50		0.33	0.71	-0.05	0.088	
T.Prot. sec				9.00	10.00	9.00		9.33	10.77	7.90	0.333	

DATA: 27/9/76

C.R.F.  
consorzio ricerca farmaceutica s.p.a.  
di Alfredo Manzato



consorzio ricerca  
farmaceutica s.p.a.

TIME = 1 MONTH

45

GROUP	VI	SEX	F	STRAIN	BEAGLE	EXPERIMENT	026	TREATMENT	CONTROLS	PHYSIOL	SOL	HEMATOLOGIC CARD		
								1.	2.	3.	M.	L.F.		
												±E.S.		
HCT %								51.00	52.00	50.00	51.00	53.48	48.52	0.577
Leuk. x1.000								7.40	8.40	7.50	7.77	9.13	6.40	0.318
Hb g/ml								15.40	16.00	14.00	15.13	17.68	12.58	0.593
Erythrocy. x Millions								7.40	7.60	8.00	7.67	8.43	6.91	0.176
MCV								69.90	68.40	62.50	66.93	76.65	57.22	2.259
FORMULA														
Neutr.								65.00	68.00	70.00	67.67	73.92	61.41	1.453
Lymph.								35.00	30.00	20.00	28.33	47.31	9.36	4.410
Mon.								0.00	0.00	0.00	0.00	0.00	0.00	0.000
Eosin.								0.00	2.00	10.00	4.00	17.14	-9.14	3.055
Basof.								0.00	0.00	0.00	0.00	0.00	0.00	0.000
Plat. x1.000								280.00	335.00	285.00	300.00	375.55	224.45	17.559
Ret. mmc								0.40	0.70	0.40	0.50	0.93	0.07	0.100
T.Prot . sec								9.50	8.50	10.00	9.33	11.23	7.44	0.441

DATA: 27/9/76

FIRMA:

C. R. F.  
CONSORZIO RICERCA PHARMACEUTICA S.p.A.  
Dr. Alfredo Nunziata

C.R.F.

## TOXICOLOGICAL DEPARTMENT

1 MONTH

	ABSOLUTE AUTOPTIC VALUES	GROUP I	ANALYSIS OF VARIANCE	EXPERIMENT	n 026	SEX M	STRAIN Beagle	46
	GROUP	GROUP III	GROUP	V	F	SIGNI.		
Brain	g	72.767 ± 4.8790	77.767 ± 8.4669	73.067 ± 5.0532	0.19	N.S.		
Hypophysis	g	0.080 ± 0.0265	0.061 ± 0.0066	0.081 ± 0.0159	0.37	N.S.		
Thymus	g	11.500 ± 0.6658	13.233 ± 0.4333	10.633 ± 1.6576	1.55	N.S.		
Heart	g	65.367 ± 1.8836	80.133 ± 4.3456	72.867 ± 4.5168	3.81	N.S.		
Liver	g	320.967 ± 43.9641	297.300 ± 14.0201	250.967 ± 20.4695	1.49	N.S.		
Spleen	g	47.567 ± 16.2071	65.300 ± 25.8931	73.567 ± 14.1117	0.46	N.S.		
Suprarenal glands	g	1.100 ± 0.0577	1.100 ± 0.1000	1.233 ± 0.0882	0.84	N.S.		
Kidneys	g	54.167 ± 3.5352	52.133 ± 3.6997	46.933 ± 4.0548	0.97	N.S.		
Gonades	g	6.300 ± 2.1733	6.633 ± 0.2963	4.033 ± 1.0682	1.00	N.S.		
Seminal vesicles	g	=	=	=				
Prostate or Uterus	g	1.833 ± 0.4372	2.000 ± 0.404	1.300 ± 0.2309	0.97	N.S.		
Weight at death	g	9033.333 ± 12.8937	9700.000 ± 68.6241	8566.667 ± 36.4492	0.46	N.S.	C. R. F. CONSORZIO RICERCA FARMACEUTICA S.p.A. <i>Alfonso Gori</i>	

+ Significant group compared to the last one.

Data: 27/9/76

Firma

C.R.F.

## TOXICOLOGICAL DEPARTMENT

1 MONTH

47

ABSOLUTE AUTOPHTIC VALUES			ANALYSIS OF VARIANCE			EXPERIMENT	1026	SEX	F	STRAIN	Beagle
	GROUP	II	GROUP	IV	GROUP	VI	GROUP		F	Signif.	+
Brain	g	75.100 ± 3.1097		74.567 ± 0.6333		79.500 ± 1.4189		1.81	N.S.	2	
Hypophysis	g	0.057 ± 0.008		0.046 ± 0.008		0.058 ± 0.0028		1.69	N.S.		
Thymus	g	8.133 ± 1.3195		13.150 ± 1.8500		9.200 ± 0.9452		3.51	N.S.		
Heart	g	74.733 ± 5.4297		59.800 ± 3.3005		69.067 ± 4.2858		2.90	N.S.		
Liver	g	262.967 ± 10.0240		221.833 ± 17.5237		204.300 ± 9.5720		4.87	N.S.	1	
Spleen	g	52.500 ± 17.905		45.167 ± 14.9279		43.433 ± 9.7381		0.10	N.S.		
Suprarenal glands	g	1.000 ± 0.1528		1.167 ± 0.0667		1.100 ± 0.0577		0.67	N.S.		
Kidneys	g	44.267 ± 3.6671		37.933 ± 4.4596		38.900 ± 1.0717		1.01	N.S.		
Gonades	g	0.733 ± 0.0333		0.600 ± 0.0577		0.567 ± 0.0333		4.20	N.S.	1	
Seminal vesicles	g	=		=		=					
Prostate; dr-Uterus	g	2.500 ± 0.7767		1.933 ± 0.1202		1.767 ± 0.1202		0.70	N.S.		
Weight at death	g	8033.333 ± 48.7359		6533.333 ± 80.7402		7733.333 ± 36.4492		2.30			

+ Significant group compared to the last one.

Data - 27/9/76

Firma

R. F.  
Consiglio Superiore di Sanitá e Medicina del Lavoro  
Dr. Alfredo Nunziata

C.R.F.

## TOXICOLOGICAL DEPARTMENT

RELATIVE AUTOPHTIC VALUE

## ANALYSIS OF VARIANCE

EXPERIMENT

n 026

SEX M

1 MONTH

STRAIN Beagle

48

GROUP

I

GROUP

III

GROUP

V

F

SIGNI.

Brain	g	$0.852 \pm 0.1760$	$0.798 \pm 0.0416$	$0.860 \pm 0.0882$	0.086	N.S.
Hypophysis	g	$0.909 \pm 0.2921$	$0.639 \pm 0.1007$	$0.926 \pm 0.1220$	0.70	N.S.
Thymus	g	$0.131 \pm 0.0162$	$0.138 \pm 0.0121$	$0.126 \pm 0.0233$	0.10	N.S.
Heart	g	$0.746 \pm 0.0830$	$0.827 \pm 0.0092$	$0.855 \pm 0.0636$	0.87	N.S.
Liver	g	$3.561 \pm 0.1381$	$3.076 \pm 0.1590$	$2.924 \pm 0.086$	6.46	0.05
Spleen	g	$0.527 \pm 0.1712$	$0.656 \pm 0.2322$	$0.860 \pm 0.1644$	0.76	N.S.
Suprarenal glands	g	$12.713 \pm 2.0154$	$11.442 \pm 1.3234$	$14.407 \pm 0.6216$	1.07	N.S.
Kidneys	g	$0.616 \pm 0.0683$	$0.539 \pm 0.0389$	$0.549 \pm 0.0411$	0.65	N.S.
Gonades	g	$0.078 \pm 0.0368$	$0.069 \pm 0.0062$	$0.048 \pm 0.0145$	0.43	N.S.
Seminal vesicles		=	=	=		
Prostate or Uterus	g	$0.020 \pm 0.0030$	$0.021 \pm 0.0042$	$0.015 \pm 0.0033$	0.66	N.S.
Weight at death	g	=	=	=		

+ Significant group compared to the last one.

Data: 27/9/76

Firma

C.R.F.  
SOCIETÀ DI RICERCA E FARMACEUTICA SPA  
A. G. M. - Milano Novembre

C.R.F.		TOXICOLOGICAL DEPARTMENT				EXPERIMENT n 026	SLX	F	STRAIN Beagle	1 MONTH					
RELATIVE AUTOPHTIC VALUES		ANALYSIS OF VARIANCE		GROUP	VI										
	GROUP	II	IV												
Brain	g	0.945 ± 0.0853	1.153 ± 0.0799	1.037 ± 0.0683	1.78	N.S.									
Hypophysis	g	0.722 ± 0.0740	0.701 ± 0.1019	0.760 ± 0.0509	0.12	N.S.									
Thymus	g	0.102 ± 0.0174	0.187 ± 0.0211	0.119 ± 0.0057	7.59	0.05	2								
Heart	g	0.930 ± 0.0041	0.919 ± 0.0383	0.896 ± 0.0407	0.28	N.S.									
Liver	g	3.287 ± 0.1055	3.393 ± 0.0392	2.712 ± 0.1664	9.9	0.05	1 2								
Spleen	g	0.640 ± 0.1843	0.693 ± 0.2122	0.583 ± 0.1716	0.08	N.S.									
Suprarenal glands	g	12.525 ± 1.9780	18.013 ± 1.3759	14.451 ± 1.7346	2.62	N.S.									
Kidneys	g	0.550 ± 0.0152	0.581 ± 0.0547	0.509 ± 0.0469	0.72	N.S.									
Gonades	g	0.009 ± 0.0003	0.009 ± 0.0003	0.007 ± 0.0001	14.93	0.01	1 2								
		=	=	=	=										
Seminal vesicles	g	=	=	=	=										
Prostate or uterus	g	0.031 ± 0.0095	0.030 ± 0.0038	0.023 ± 0.0016	0.53	N.S.									
Weight at death	g	=	=	=	=										
+ Significant group compared to the last one.															
						Data: 27/9/76	Firma	C. R. F. INDUSTRIAS INERICA FARMACEUTICA S.A. Atenas - Guatemala							



**CRF**  
consorzio ricerca  
farmaceutica s.p.a.

Volume Formulas and Area Formulas

1 MONTI

50

	N	I	SEX	M	STRAIN	Beagle	EXPERIMENT	O26	TREATMENT	200Mg/Kgin2ml/Kg.	AUTOPTIC CARD				
Animal	.		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	M.	L.F.	tE.S.
Breast	g	184.700	64.900	71.700									72.707	93.75951.774	4.8790
	gt	1.184	0.585	0.788									0.852	1.609 0.095	0.1760
Hypophysis	g	0.055	0.052	0.133									0.080	0.198-0.034	0.0265
	gt	0.797	0.468	1.462									0.909	2.166-0.348	0.2921
Thymus	g	10.600	11.100	12.800									11.500	14.365 8.635	0.6658
	gt	0.154	0.100	0.141									0.131	0.201 0.062	0.0162
Heart	g	61.600	67.200	67.300									65.367	73.4 157.262	1.8836
	gt	0.893	0.605	0.740									0.746	1.103 0.389	0.0730
Liver	g	258.000405.600299.300											320.967	510.13131.802	43.9641
	gt	3.739	3.654	3.289									3.561	4.155 2.967	0.1381
Spleen	g	25.300	38.300	79.100									47.567	117.30122.168	16.2071
	gt	0.387	0.345	0.869									0.527	1.264-0.210	0.1712
Suprarenal glands	g	1.100	1.000	1.200									1.100	1.348 0.852	0.0577
	gt	15.942	9.009	13.187									12.713	21.384 4.041	2.0154
Kidneys	g	51.900	61.100	49.500									54.167	69.37838.956	3.5352
	gt	0.752	0.550	0.544									0.616	0.910 0.321	0.0683
Gonades	g	10.400	5.500	3.000									6.300	15.651-3.051	2.1733
	gt	0.151	0.050	0.033									0.078	0.236-0.081	0.0368
Seminal vesicles	g	=	=	=											
	gt	=	=	=											
Prostate or Uterus	g	1.500	2.700	1.300									1.833	3.714-0.048	0.4372
	gt	0.022	0.024	0.014									0.020	0.033 0.007	0.0030
Weight at death	g	6900	11100	9100									9033	14252 3815	1212.9

DATA: 27/9/78

FIRMA: CANTIERE RICERCA FARMACEUTICA S.p.A.  
Dr. Alfredo Nunziata



**CRF**  
Corporzio ricerca  
farmaceutica s.p.a.

1 MONTH

51

Animal	N	II	SEX	F	STRAIN	Beag.	EXPERIMENT	026	TREATMENT	.200mg/Kg in 2ml/Kg		AUTOPTIC CARD		
										ev	M.	L.F.	±E.S.	
Brain	g	77.100	69.000	F	79.200	-	-	-	-	=	75.100	88.480	61.720	3.1097
	g%	0.857	0.863		1.115	-	-	-	-	=	0.945	1.312	0.578	0.0753
Hypophysis	g	0.060	0.049	F	0.063	-	-	-	-	=	0.057	0.076	0.039	0.0043
	g%	0.667	0.613		0.887	-	-	-	-	=	0.722	1.074	0.361	0.0840
Thymus	g	9.600	5.500	F	9.300	-	-	-	-	=	8.133	13.811	2.456	1.3195
	g%	0.107	0.069		0.131	-	-	-	-	=	0.102	0.180	0.024	0.0181
Heart	g	84.300	74.400	F	65.500	-	-	-	-	=	74.733	94.095	51.371	5.4297
	g%	0.937	0.930		0.923	-	-	-	-	=	0.930	0.947	0.912	0.0041
Liver	g	277.400	267.800	F	243.700	-	-	-	-	=	262.967	306.097	19.836	10.0240
	g%	3.082	3.348		3.432	-	-	-	-	=	3.287	3.741	2.834	0.1055
Spleen	g	86.700	26.000	F	44.800	-	-	-	-	=	52.500	129.693	24.693	17.905
	g%	0.963	0.325		0.631	-	-	-	-	=	0.640	1.433	0.153	0.1843
Suprarenal glands	g	1.200	0.700	F	1.100	-	-	-	-	=	1.000	1.657	0.343	0.1528
	g%	11.333	8.750		15.493	-	-	-	-	=	12.525	21.079	3.972	1.9880
Kidneys	g	51.500	41.700	F	39.600	-	-	-	-	=	44.267	60.0	528.488	3.6671
	g%	0.572	0.521		0.558	-	-	-	-	=	0.550	0.616	0.485	0.0152
Gonades	g	0.800	0.700	F	0.700	-	-	-	-	=	0.733	0.877	0.590	0.0333
	g%	0.009	0.009		0.010	-	-	-	-	=	0.009	0.011	0.007	0.0003
Seminal Vesicles	g	-	-	F	-	-	-	-	-	-	-	-	-	C. P. F.
	g%	-	-		-	-	-	-	-	-	-	-	-	
Prostate or Uterus	g	2.100	4.000	F	1.400	-	-	-	-	=	2.500	5.842	-0.842	0.7767
	g%	0.023	0.050		0.020	-	-	-	-	=	0.031	0.072	-0.010	0.0095
Weight at death	g	9000	8000	F	7100	-	-	-	-	=	8033	10394	5672	548.7

DATA: 27/9/76

FIRMA: DR. S. NUNZIATA

Dr. Alfredo Nunziata



**consorzio ricerca  
farmaceutico s.p.a.**

L'EUR - ROMA - Via Trieste 14  
Telefono 06 646 012064 321061

1 MONTH

52

Animal	N	III	SEX	M	STRAIN	Beag.	EXPERIMENT	026	TREATMENT	·100mg/Kg in 2ml/Kg ev		AUTOPHTIC CARD			
										1.	2.	3.	4.	5.	
Brain	g	69.400	69.200	94.700						=	=	=	=	77.767	114.19741.336
	g%	0.780	0.736	0.877						=	=	=	=	0.798	0.9% 0.619
Hypophysis	g	0.074	0.056	0.053						=	=	=	=	0.061	0.079 0.033
	g%	0.831	0.596	0.491						=	=	=	=	0.639	1.073 0.206
Thymus	g	14.000	13.200	12.500						=	=	=	=	13.233	15.097 11.369
	g%	0.157	0.140	0.116						=	=	=	=	0.138	0.190 0.076
Heart	g	73.000	79.400	88.000						=	=	=	=	80.133	98.83161.435
	g%	0.820	0.845	0.815						=	=	=	=	0.827	0.866 0.787
Liver	g	270.100316.800305.000								=	=	=	=	297.300	357.62436.976
	g%	3.035	3.370	2.824						=	=	=	=	3.0% 3.761	2.392 0.1590
Spleen	g	62.900	21.700111.300							=	=	=	=	65.300	176.71046.110
	g%	0.70	0.231	1.031						=	=	=	=	0.656	1.655-0.343
Suprarenal glands	g	1.000	1.300	1.000						=	=	=	=	1.100	1.530 0.670
	g%	11.236	13.830	9.259						=	=	=	=	11.442	17.136 5.747
Kidneys	g	54.400	44.900	57.100						=	=	=	=	52.133	68.05236.215
	g%	0.611	0.478	0.529						=	=	=	=	0.539	0.707 0.372
Gonades	g	7.200	6.200	6.500						=	=	=	=	6.633	7.908 5.359
	g%	0.081	0.066	0.060						=	=	=	=	0.069	0.096 0.042
Seminal Vesicles	g	=	=	=						=	=	=	=		
	g%	=	=	=						=	=	=	=		
Prostate or Uterus	g	1.300	2.700	2.000						=	=	=	=	2.000	3.739 0.261
	g%	0.015	0.029	0.019						=	=	=	=	0.021	0.039 0.003
Weight at death	g	8900	9400	10800						=	=	=	=	9700	12147 7253 568.6

C.R.F.  
DATA: 27/9/76

FIRMA: *consorzio ricerca farmaceutico s.p.a.*  
*Dr. Alfredo Nunziata*



**CRF**  
consorzio ricerca  
farmaceutica s.p.a.

I MONTI

53

Animal	N	IV	SEX	F	STRAIN	Beag.	EXPERIMENT	026	TREATMENT	100mg/Kg in 2ml/Kg. ev				AUTOPTIC CARDS								
										1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	M.	L.F.	S.E.S.
Brown				g	75.200	73.300	75.200			=	=	=	=	=	=	=	=	=	=	74.567	77.29271.842	0.6333
				g%	1.106	1.309	1.044			=	=	=	=	=	=	=	=	=	=	1.153	1.497 0.809	0.0799
Hypophysis				g	0.033	0.04	0.060			=	=	=	=	=	=	=	=	=	=	0.046	0.079 0.012	0.0078
				g%	0.485	0.786	0.833			=	=	=	=	=	=	=	=	=	=	0.701	1.170 0.233	0.1089
Thymus				g	11.300	=	15.000			=	=	=	=	=	=	=	=	=	=	13.150	21.110 5.190	1.8500
				g%	0.166	=	0.208			=	=	=	=	=	=	=	=	=	=	0.187	0.278 0.097	0.0211
Heart				g	58.000	55.200	66.200			=	=	=	=	=	=	=	=	=	=	59.800	74.00145.599	3.3005
				g%	0.853	0.986	0.919			=	=	=	=	=	=	=	=	=	=	0.919	1.084 0.754	0.0383
Liver				g	235.900	187.000	242.600			=	=	=	=	=	=	=	=	=	=	221.833	297.23346.434	17.5227
				g%	3.469	3.339	3.369			=	=	=	=	=	=	=	=	=	=	3.393	3.561 3.224	0.0392
Spleen				g	19.000	45.800	70.700			=	=	=	=	=	=	=	=	=	=	45.167	109.39719.063	14.9279
				g%	0.279	0.818	0.982			=	=	=	=	=	=	=	=	=	=	0.693	1.606-0.220	0.2122
Suprarenal glands				g	1.300	1.100	1.100			=	=	=	=	=	=	=	=	=	=	1.167	1.454 0.880	0.0667
				g%	19.118	19.643	15.278			=	=	=	=	=	=	=	=	=	=	18.013	23.93312.093	1.3759
Kidneys				g	46.500	31.500	35.800			=	=	=	=	=	=	=	=	=	=	37.933	57.12218.745	4.4596
				g%	0.684	0.563	0.497			=	=	=	=	=	=	=	=	=	=	0.581	0.816 0.346	0.0547
Gonades				g	0.600	0.500	0.700			=	=	=	=	=	=	=	=	=	=	0.600	0.848 0.352	0.0577
				g%	0.009	0.009	0.010			=	=	=	=	=	=	=	=	=	=	0.009	0.010 0.008	0.0003
Seminal Vesicles				g	=	=	=			=	=	=	=	=	=	=	=	=	=			
				g%	=	=	=			=	=	=	=	=	=	=	=	=	=			
Prostate or Uterus				g	1.700	2.100	2.000			=	=	=	=	=	=	=	=	=	=	1.933	2.450 1.416	0.1202
				g%	0.025	0.038	0.028			=	=	=	=	=	=	=	=	=	=	0.030	0.036 0.014	0.0038
Weight at death				g	6800	5600	7200			=	=	=	=	=	=	=	=	=	=	6533	8602 4465	480.7
																				C.R.F.		

DATA: 27/9/76 FIRMA: CONSORZIO BANCARO FINANZIARIO SPA  
Dr. Alfredo Nanzola





**CRP**  
consorzio ricerca  
farmaceutica s.p.a.

1 MONTH

55

N	W	LX	F	SHAIN Beag.	EXPERIMENT	026	TREATMENT	PHYSOL. SOL.	.in2 ml/Kg	AUTOPTIC CARD	ev				
Animal	.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	M.	L.F.	<u>E.S.</u>	
Brain	g	78.500	82.300	77.700	=	=	=	=	=	=	=	79.500	85.60573.395	1.4189	
	g%	0.924	1.029	1.160	=	=	=	=	=	=	=	1.037	1.331	0.743	0.0683
Hypophysis	g	0.056	0.064	0.055	=	=	=	=	=	=	=	0.058	0.071	0.046	0.0028
	g%	0.659	0.800	0.821	=	=	=	=	=	=	=	0.760	0.979	0.541	0.0509
Thymus	g	11.000	8.800	7.800	=	=	=	=	=	=	=	9.200	13.267	5.133	0.952
	g%	0.129	0.110	0.116	=	=	=	=	=	=	=	0.119	0.143	0.094	0.0057
Heart	g	77.600	65.500	64.100	=	=	=	=	=	=	=	69.067	87.50750.626	4.2858	
	g%	0.913	0.819	0.957	=	=	=	=	=	=	=	0.896	1.071	0.721	0.0407
Liver	g	202.500	27.000	195.400	=	=	=	=	=	=	=	208.300	249.48567.115	9.5720	
	g%	2.382	2.838	2.916	=	=	=	=	=	=	=	2.712	3.428	1.996	0.1664
Spleen	g	40.700	28.100	61.500	=	=	=	=	=	=	=	43.433	85.334	1.533	9.7381
	g%	0.479	0.351	0.918	=	=	=	=	=	=	=	0.583	1.321	-0.156	0.1716
Suprarenal glands	g	1.100	1.000	1.200	=	=	=	=	=	=	=	1.100	1.348	0.852	0.0577
	g%	12.981	12.500	17.910	=	=	=	=	=	=	=	14.451	21.914	6.987	1.7346
Kidneys	g	39.500	36.800	40.400	=	=	=	=	=	=	=	38.900	43.55434.246	1.017	
	g%	0.465	0.460	0.603	=	=	=	=	=	=	=	0.509	0.711	0.307	0.0469
Gonads	g	0.600	0.600	0.500	=	=	=	=	=	=	=	0.567	0.710	0.423	0.0333
	g%	0.007	0.008	0.007	=	=	=	=	=	=	=	0.007	0.007	0.007	0.0001
Seminal Vesicles	g	=	=	=	=	=	=	=	=	=	=				
	g%	=	=	=	=	=	=	=	=	=	=				
Prostate or Uterus	g	2.000	1.600	1.700	=	=	=	=	=	=	=	1.767	2.284	1.250	0.1202
	g%	0.024	0.020	0.025	=	=	=	=	=	=	=	0.023	0.030	0.016	0.0016
Weight at death	g	8500	8000	6700	=	=	=	=	=	=	=	7733	10042	5425	536.4

DATA: 27/9/76

FIRMA:

CRP F  
consorzio ricerca farmaceutica s.p.a.  
Dr. Alfredo Nunziata



CBF  
Consorzio ricerca  
farmaceutico S.p.A.

00140 Roma (Roma) via 12 Settembre  
Telefono 06 20648 912108.. 912109

TIME 0

56

GROUP I SEX M STRAIN Beagle EXPERIMENT 026 TREATMENT 200mg/Kg in 2ml/Kg ev. BIOCHEMICAL CARD

		1.	2.	3.	M.	L.F.	$\pm$ E.S.
CO <sub>2</sub>	meq/l	24.00	20.00	20.00	21.33	27.07	15.60
Prot. Tot.	g%	8.90	7.80	8.00	8.23	9.69	6.78
Albumin	g%	4.70	4.10	4.20	4.33	5.13	3.54
Inorg. P.	mg%	10.00	10.00	10.00	10.00	10.00	10.00
Cholest.	mg%	155.00	165.00	140.00	153.33	184.57	122.09
Glucos	c mg%	120.00	130.00	145.00	131.67	152.91	100.43
BUN	mg%	10.70	11.60	13.00	11.77	14.64	8.89
Billirub.T.	mg%	0.50	0.40	0.50	0.47	0.61	0.32
Alk.phosph-mU/ml	285.00	245.00	185.00	238.33	363.29	113.38	29.059
LDH	mmU/m	0.60	0.23	0.30	0.38	0.87	-0.12
SGPT	mU/ml	30.00	25.00	25.00	26.67	33.83	19.50
SGOT	mU/ml	110.00	55.00	60.00	75.00	150.51	-0.51
C1 ion	meq/l	130.00	130.00	127.00	129.00	133.30	124.70
Na ion	meq/l	167.00	166.00	134.00	155.67	202.27	109.07
K ion	meq/l	6.90	6.10	4.80	5.93	8.56	3.30
Ca <sup>++</sup>	mg%	12.00	12.80	12.00	12.27	13.41	11.12

DATA: 27/9/76

C.R.F.  
CONSORZIO RICERCA FARMACEUTICO  
FIRMA: Dr. Alfredo Nurzia



**Consortio ricerca  
industria e p.a.**

00000 - 01.002.3 (R) 00000000000000000000000000000000

TIME: ( )

57

DATA: 27/9/71

C. R. F.  
CONSORZIO INDUSTRIALE NEOPOLITANO S.p.A.  
Dg. Alfredo Nunziata



**CRF**  
consorzio ricerca  
farmaceutica s.p.a.

6004, 2011-2d Hulme, 13 T.C.Sher.  
1226, 42-212 212-4 - 212

58

TIME: 0

DATA: 27/9/76

C. R. F.  
FIRMA: ~~COMPAÑIA MEXICANA FARMACEUTICA~~  
Dr. Alfredo Nurzia



**CRP**  
consorzio ricerca  
farmaceutica s.p.a.

00044 Perugia (Provincia di Terni) - post. 15  
Telefono 9-25048 - 9121064 - 9121065

TIME: 0

59

**CRF**consorzio ricerca  
farmaceutica s.p.a.Corso Fumagalli 10 - 20133 Milan  
Milano 9120649 921084 91210

TIME = 0

**60**

GROUP V SEX M STRAIN Beagle EXPERIMENT 026 TREATMENT PHYSIOL SOL. in 2 ml/Kg<sub>v</sub> BIOCHEMICAL CARD

		1.	2.	3.	M.	L.F.	<u>E.S.</u>
C02	meq/l	23.00	21.00	23.00	22.33	25.20	19.46
Prot.Tot.	g%	8.10	8.60	8.80	8.50	9.40	7.60
Albumine	g%	4.70	4.50	5.00	4.73	5.36	4.11
Inorg. P.	mgt	8.30	8.70	9.40	7.80	10.18	7.42
Cholest.	mgt	175.00	170.00	200.00	181.67	221.59	141.74
Glucose	mgt	145.00	135.00	145.00	141.67	156.01	127.32
BUN	mgt	10.30	10.70	12.20	11.07	13.55	8.58
Bilirub.T.	mgt	0.60	0.50	0.40	0.50	0.75	0.25
Alk.phosn	mU/ml	220.00	370.00	350.00	313.33	515.66	111.01
LDH	mmU/ml	0.23	0.20	0.15	0.19	0.29	0.10
SGPT	mU/ml	35.00	35.00	25.00	31.67	46.01	17.32
SGOT	mU/ml	55.00	60.00	50.00	55.00	67.42	42.58
Cl ion	meq/l	140.00	125.00	128.00	131.00	150.72	111.28
Na ion	meq/l	150.00	125.00	129.00	134.67	168.03	101.31
K ion	meq/l	5.40	4.10	4.10	4.53	6.40	2.67
Ca++	mgt	13.10	12.10	13.70	12.97	14.97	10.96

DATA: 27/9/76

C.R.F.  
CONSORZIO RICERCA FARMACEUTICA S.p.A.  
FIRMA: Dr. Alfredo Nunziata

ISCRIZIONE RICERCA  
INNOVACUTA S.p.A.

TIME = 0

61

GROUP VI SLX F STRAIN Beagle EXPERIMENT 026 TREATMENT PHYSIOL. SOL. IN 2 ml/Kg ev. BIOCHEMICAL CARD

		1.	2.	3.	M.	L.F.	<u>S.E.S.</u>
CO <sub>2</sub>	meq/l	22.00	27.00	22.00	23.67	30.84	16.50
Prot. Tot.	g%	8.40	9.00	8.80	8.73	9.49	7.97
Albumino	g%	5.10	5.30	4.50	4.97	6.00	3.93
Inorg. P.	mgt	9.20	9.80	9.20	9.40	10.26	8.54
Cholest.	mgt	145.00	195.00	150.00	163.33	231.74	98.92
Glucosce	mgt	140.00	120.00	155.00	138.33	181.95	94.71
BUN	mgt	16.60	12.40	12.70	13.90	19.72	8.08
Bilirub.T.	mgt	0.50	0.40	0.40	0.43	0.58	0.29
Alk.phosphat	U/ml	200.00	245.00	205.00	216.67	277.94	155.40
LDH	mU/ml	110.00	150.00	275.00	178.33	392.15	-35.48
SGPT	mU/ml	40.00	35.00	25.00	33.33	52.31	14.36
SGOT	mU/ml	60.00	55.00	80.00	65.00	97.86	32.14
Cl ion	meq/l	136.00	150.00	187.00	144.33	162.64	126.02
Na ion	meq/l	125.00	154.00	154.00	144.33	185.93	102.74
K ion	meq/l	3.70	5.00	5.00	4.57	6.43	2.70
Ca <sup>++</sup>	mgt	12.90	14.50	12.50	13.30	15.93	10.67

DATA: 27/9/76

C.R.F.  
CONS. INNOVACUTA S.p.A.  
Dr. Alfredo Nunziata

CRP

CONSO 12.0.6.21.22  
Agosto 1976

TIME: 0

62

TABLE I - IN M LIGAN Beagle EXPERIMENT 026 DOSE: 200mg/Kg + ml/Kg ev. REMEDICAL AGO

	1.	2.	3.	M.	L.F.	±E.S.
HCT %	40.00	42.00	40.00	40.67	43.53	37.80
Leuk. x1.000	12.20	9.20	9.20	10.20	14.50	5.90
Hb g/ml	10.80	12.40	10.80	11.33	13.63	9.04
Rythm. x1.000	6.50	7.00	7.00	6.83	7.55	6.12
M.V.	61.50	60.00	57.10	59.53	65.09	53.97
FORMULA						
Neutr.	42.00	40.00	44.00	42.00	46.97	37.03
Lymph.	46.00	40.00	54.00	46.67	64.10	29.23
Mon.	2.00	12.00	2.00	5.33	19.67	-9.00
Eosin.	10.00	8.00	0.00	6.00	19.14	-7.14
Basof.	0.00	0.00	0.00	0.00	0.00	0.000
Plat. x1.000	1140.00	750.00	365.00	785.00	1433.57	336.43
Ret. mmc	0.70	0.30	1.00	0.67	1.54	-0.21
T.Prot. sec	6.50	1.90	9.00	7.80	10.91	4.69
						0.723

C/R.  
DATA: 27/9/76

FIRMA: CONSELLERIA PHARMAUTICA S.p.A.  
Dr. Alfredo Nunziata

CRP  
consiglio regalo  
carica attiva s.p.a.

TIME = 0

63

GROUP II SEX F STRAIN Beagle EXPERIMENT 026 TREATMENT 200mg/Kg 2 ml/Kg ev HEMATOLOGIC CARD

	1.	2.	3.	M.	L.F.	<u>S.E.S.</u>
HCT %	40.00	42.00	42.00	41.33	44.20	38.47
Leuk. x1.000	7.20	5.00	7.60	6.60	10.0	3.12
Hb g/ml	12.00	14.20	13.80	13.33	16.24	10.42
Erythrocyt. x millions	6.60	7.20	7.40	7.07	8.10	6.03
MCV	60.60	58.30	56.40	58.43	63.65	53.21

FORMULA

Neutr.	50.00	56.00	59.00	55.00	66.38	43.62	2.646
Lymph.	48.00	44.00	40.00	44.00	53.93	34.07	2.309
Mon.	2.00	0.00	1.00	1.00	3.48	-1.48	0.57
Eosin.	0.00	0.00	0.00	0.00	0.00	0.00	0.000
Basof.	0.00	0.00	0.00	0.00	0.00	0.00	0.000
Plat. x1.000	545.00	225.00	350.00	373.33	773.71	-27.04	93.110
Ret. mmc	1.60	1.00	0.70	1.10	2.24	-0.04	0.265
T.Prot . sec	8.00	11.90	7.10	7.67	8.89	6.44	0.285

DATA: 27/9/76

FIRMA: *A.R.F.  
AEROFARMA S.P.A.  
Dr. Alfredo Nunziata*

TIME = 0

64

GROUP III SIX M STRAIN Beagle EXPERIMENT 326 TREATMENT 100mg/Kg 2 ml/Kg ev HEMATOLOGIC CARD

	1.	2.	3.	M.	L.F.	<u>E.S.</u>
HCT %	44.00	41.00	45.00	43.33	48.50	38.17
Leuk. x1.000	12.40	13.00	11.00	12.13	14.68	9.59
Hb g/ml	13.50	11.80	15.00	13.43	17.41	9.46
lymphocytes millions	7.20	6.80	7.40	7.13	7.89	6.37
MCV	61.10	60.30	60.80	60.73	61.74	59.73
						0.233

## FORMULA

Plat. x1,000	550.00	675.00	390.00	538.33	892.99	183.67	82.479
Ret. mmc	0.60	0.80	0.80	0.73	1.02	0.45	0.067
T.Prot . sec	7.50	7.00	6.00	6.83	8.73	4.94	0.441

DAT: 27/9/76

C. P. F.  
CONFERIMENTO RICERCA FARMACEUTICA  
FIRMA: Dr. Alfredo Nunziata

Constituted  
July 1, 1900.

TIME = 0

65

GROUP IV SEX F STRAIN Beagle EXPERIMENT 026 TREATMENT 100mg/Kg 2 ml/Kg ev HEMATOLOGIC CARD

	1.	2.	3.	M.	L.F.	<u>E.S.</u>
HCT %	41.00	44.00	45.00	43.33	48.50	38.16
Leuc. x 1.000	8.40	12.50	8.20	9.70	15.73	3.67
Hb g/ml	12.60	14.00	14.30	13.63	15.89	11.38
hctcrit. x millions	6.80	8.00	7.00	7.27	8.86	5.67
M N	60.30	55.00	64.30	59.87	71.46	48.28
<b>FORMULA</b>						
Neutr.	67.00	73.00	61.00	67.00	81.90	52.10
Lymph.	30.00	22.00	34.00	28.67	43.85	13.49
Mon.	2.00	4.00	3.00	3.00	5.48	0.52
Eosin.	1.00	1.00	2.00	1.33	2.77	-0.10
Basof.	0.00	0.00	0.00	0.00	0.00	0.000
Plat. x 1.000	700.00	690.00	705.00	697.33	717.31	679.36
Ret. mmc	0.80	0.50	0.60	0.63	1.01	0.25
T.Prot. sec	7.30	6.90	9.00	7.73	10.50	4.96

DATA: 27/9/76

FIRMA: M. R. F.  
Alfredo Nunziata

rzio ricerca  
ceutica s.p.a.

00045 Roma via F.lli Brancati, 4  
Telefono 06/648.921064 - 921367

TIME = 0:

66

GROUP: V SEX: M STRAIN: Beagle EXPERIMENT: 026 TREATMENT: PHYSIOL. SOL. 2 ml/Kg ev HEMATOLOGIC CARD: 11

	1.	2.	3.	M.	L.F.	±E.S.	
HCT %	48.00	45.00	43.00	45.33	51.58	39.09	1.453
Leuk x1.000	6.60	8.80	7.20	7.53	10.36	4.71	0.657
Hb g/ml	14.40	15.40	13.00	14.27	17.26	11.27	0.696
Erythroc. x millions	7.00	7.60	8.60	7.73	9.74	5.73	0.467
MCV	62.80	59.20	50.00	54.33	73.72	40.95	3.811
FORMULA							
Neutr.	40.00	46.00	48.00	44.67	55.00	34.33	2.404
Lymph.	56.00	42.00	48.00	48.67	66.10	31.23	4.055
Mon.	0.00	8.00	2.00	3.33	13.67	-7.00	2.404
Eosin.	4.00	0.00	0.00	1.33	7.00	-4.40	1.333
Basof.	0.00	4.00	0.00	1.33	7.07	-4.40	1.333
Plat...x1.000	425.00	415.00	920.00	586.67	1303.44-130.11	166.692	
Ret. mmc	0.60	0.40	0.50	0.50	0.75	0.25	0.058
T.Prot. sec	8.00	8.50	9.50	8.67	10.56	6.77	0.441

DATA: 27/9/76

C. R. F.  
FIRMA: CONSORZIO RICERCA PHARMACEUTICA S.p.A.  
Dr. Alfredo Nunziata

DISCO E.O. (KOBEDO)  
C.R.F. - 67

TIME = 0

67

GROUP VI SEX F STRAIN Beagle EXPERIMENT 026 TREATMENT PHYSIOL SOL, 2 ml/Kg ev HEMATOLOGIC CARD

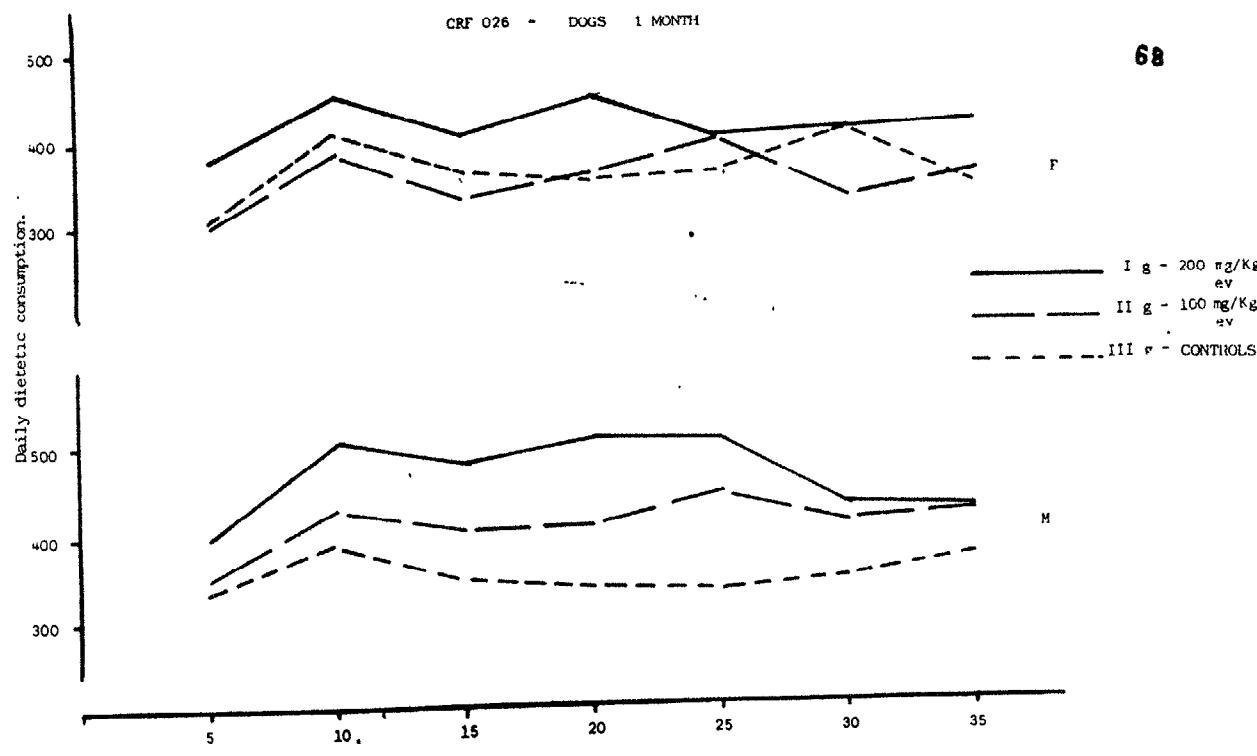
	1.	2.	3.	M.	L.F.	%E.S.
HCT %	45.00	45.00	44.00	44.67	46.10	43.23
Leuk.,x1.000	8.60	8.00	8.40	8.33	9.09	7.57
Hb g/ml	15.10	14.80	14.20	14.70	15.84	13.56
Erythroc. x millions	7.60	7.60	7.80	7.67	7.95	7.38
MCV	59.20	59.20	56.40	58.27	62.28	54.25
FORMULA						
Neutr.	35.00	35.00	55.00	41.67	70.33	13.00
Lymph.	60.00	60.00	40.00	53.33	82.00	24.67
Mon.	2.00	0.00	5.00	2.33	8.58	-3.91
Eosin.	3.00	5.00	0.00	2.67	8.91	-3.58
Basof.	0.00	0.00	0.00	0.00	0.00	0.000
Plat. x1.000	495.00	785.00	410.00	563.33	1051.46	75.21
Ret. mmic	0.50	0.70	1.20	0.80	1.70	-0.10
T.Prot. sec	8.20	8.00	7.90	8.03	8.41	7.65

DATA: 27/9/76

C. R. F.  
CENTRO DI RICERCHE FARMACEUTICHE S.p.A.  
FIRMA: *Alfredo Nazzalà*

## CRF 026 - DOGS 1 MONTH

68



TIME, DAYS

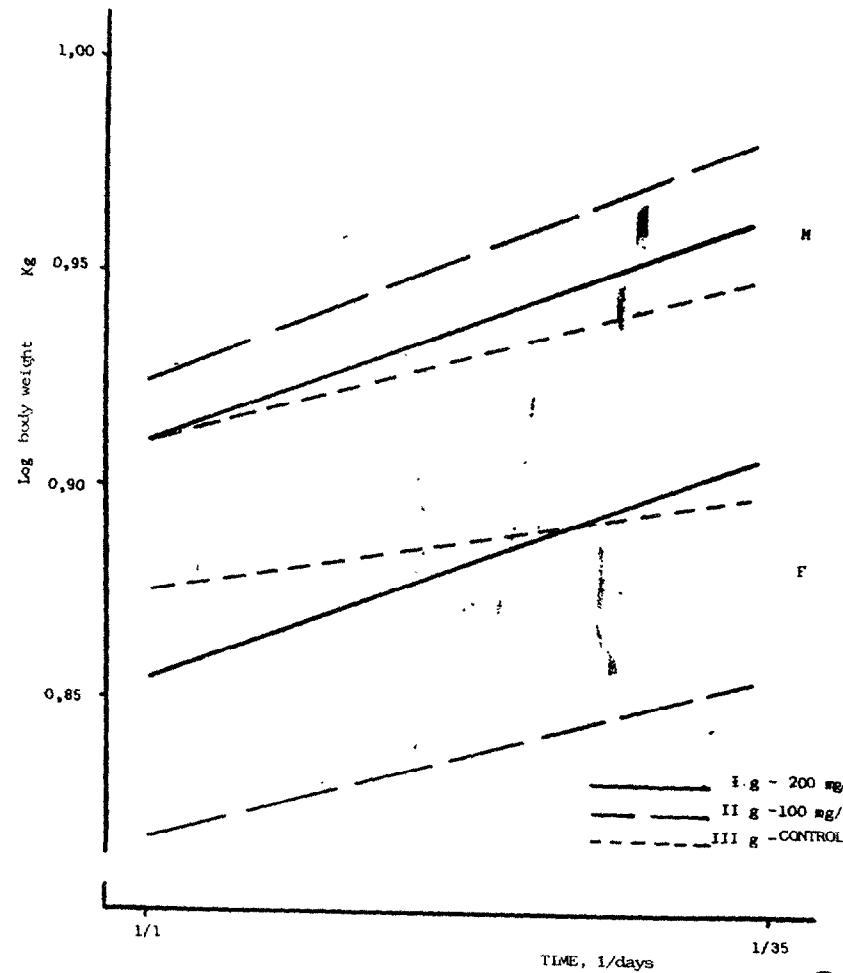
DATA: 27/9/76

FIRMA:

G. R. F.  
ARMANDO RICCI S.p.A.  
Dr. Alfredo Nunziata

CRF 026 - DOGS 1 MONTH

69



DATA: 27/9/76

FIRMA:

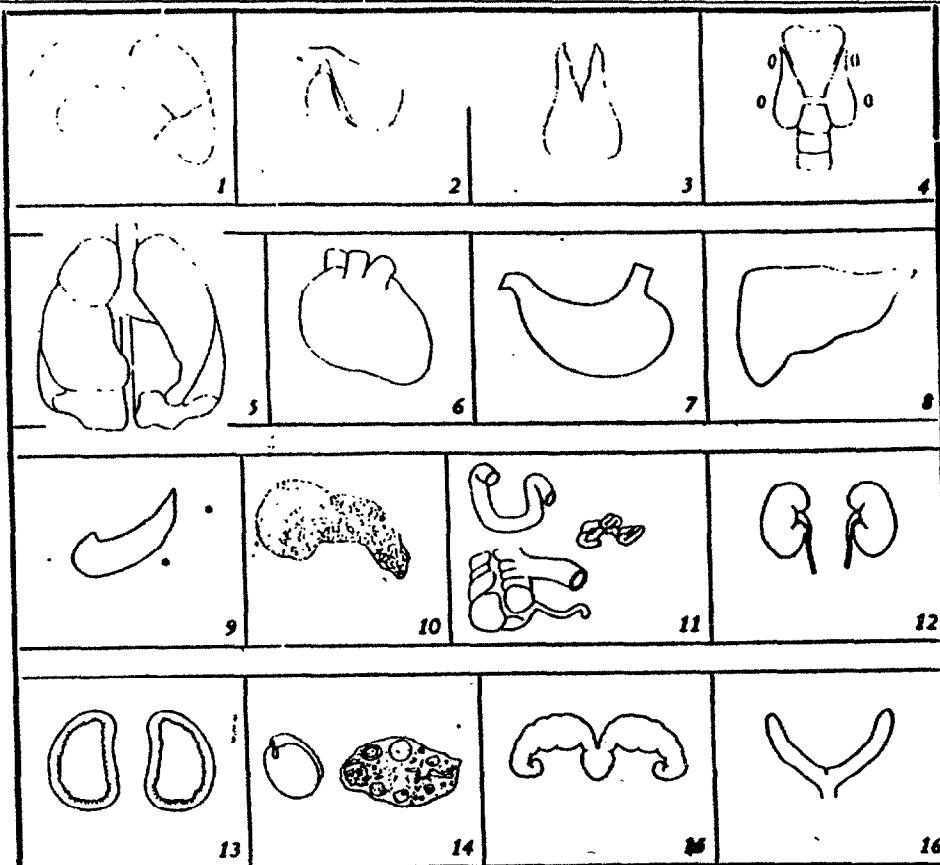
C.R.  
CONSEL  
Dr. Alfredo Nuñez  
69

TOXICOLOGICAL DEPARTMENT  
C R F

70

AUTOPTIC CARD

N 1 I	SEX M	STRAIN Beagle	EXPERIMENT 026	TREATMENT 200 mg/kg i.v.- 1 M
----------	----------	------------------	-------------------	----------------------------------



ORGAN

- |               |          |              |        |                                   |
|---------------|----------|--------------|--------|-----------------------------------|
| 1. BRAIN      | g 81,7   | 6. HEART     | g 61,6 | 11. INTESTINE                     |
| 2. HYPOPHYSIS | g 0,055  | 7. STOMACH   | g 25,8 | 12. KIDNEYS g 51,9                |
| 3. THYMUS     | mg 10600 | 8. LIVER     | g 25,3 | 13. SUPRAR. G. mg 1100            |
| 4. THYROID    | g        | 9. SPLEEN    | g 25,3 | 14. GONADS g 10,4                 |
| 5. LUNGS      |          | 10. PANCREAS |        | 15. SEMINAL VES.                  |
|               |          |              |        | 16. PROSTATE OR mg 1500<br>UTERUS |

NOTE:

Autoptic: Increased right kidney with small nickings and variegated on the surface of section

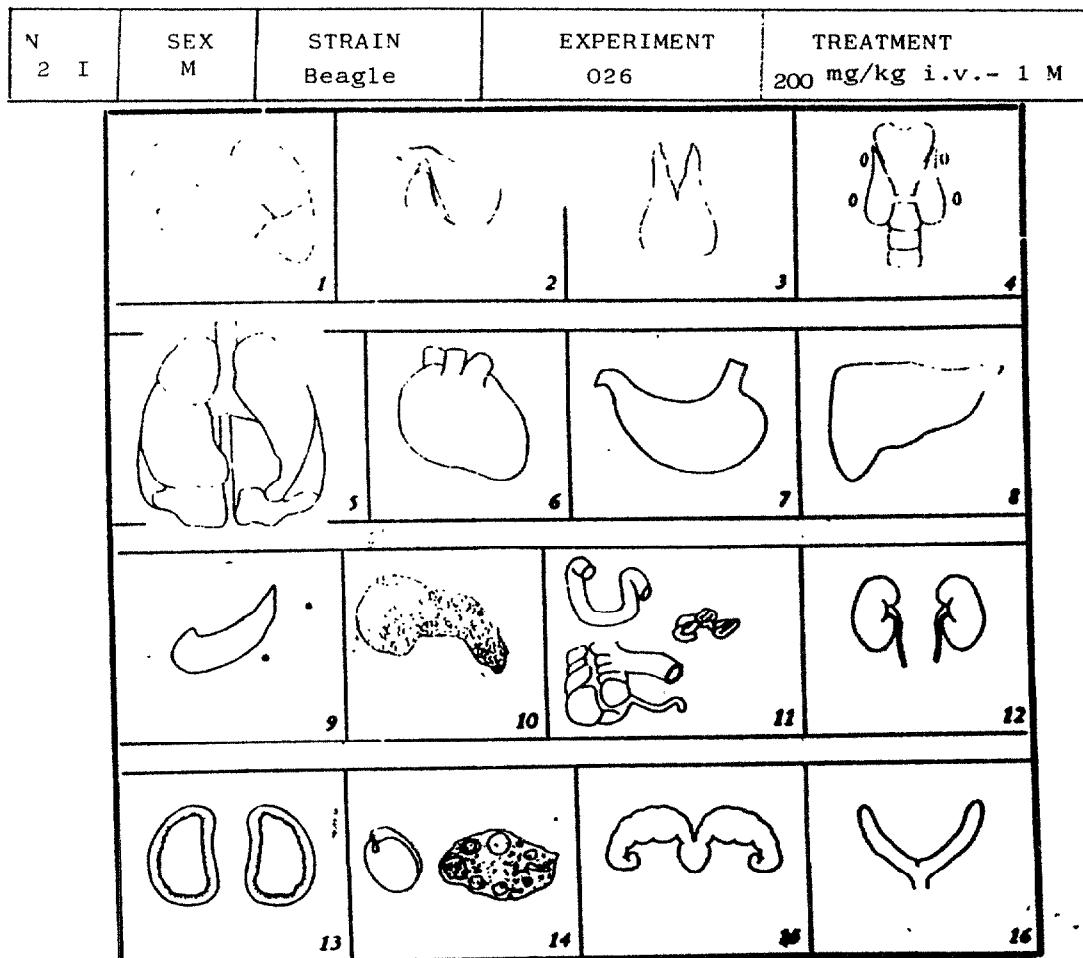
Histologic: intertubular lymphocytic infiltrations in kidney.

Date 27/9/76

TOXICOLOGICAL DEPARTMENT  
C R F

71

AUTOPTIC CARD



ORGAN

- |                       |                  |                           |
|-----------------------|------------------|---------------------------|
| 1. BRAIN g 64,9       | 6. HEART g 67,2  | 11. INTESTINE -           |
| 2. HYPOPHYSIS g 0,052 | 7. STOMACH -     | 12. KIDNEYS g 61,1        |
| 3. THYMUS mg 11100    | 8. LIVER g 405,6 | 13. SUPRAR. G.mg 1000     |
| 4. THYROID -          | 9. SPLEEN g 38,3 | 14. GONADS g 5,5          |
| 5. LUNGS              | 10. PANCREAS     | 15. SEMINAL VES.          |
|                       |                  | 16. PROSTATE OR<br>UTERUS |

NOTE:

Autoptic:

Histologic:

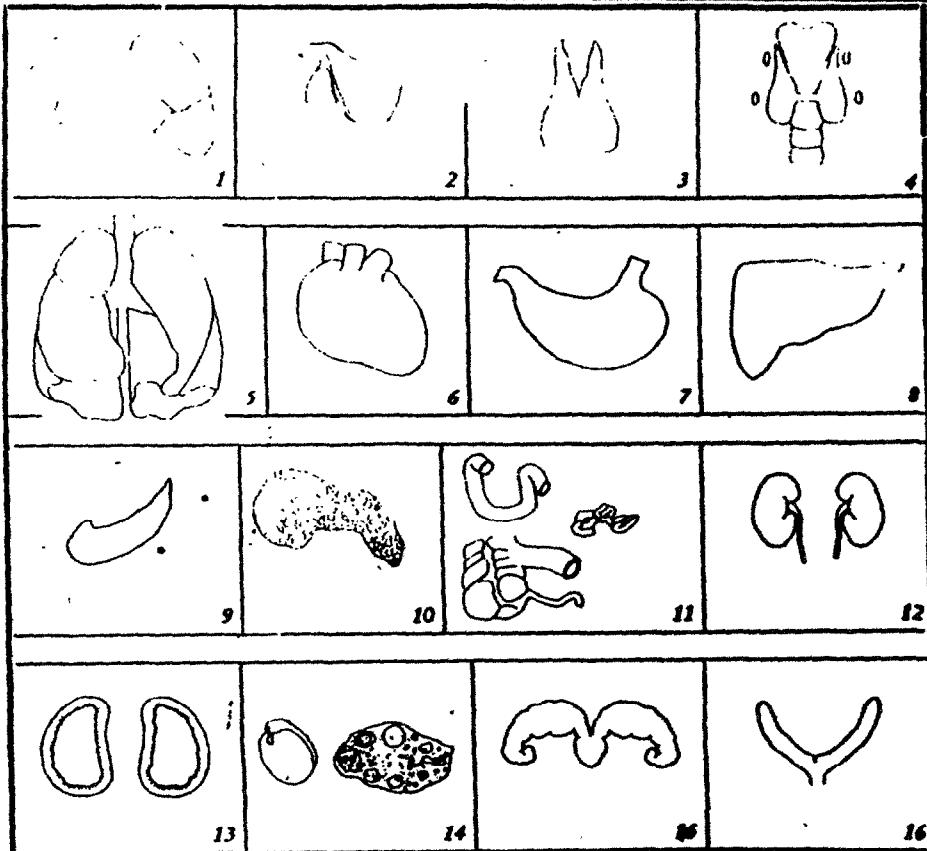
Date 27/9/76

TOXICOLOGICAL DEPARTMENT  
C R F

72

AUTOPTIC CARD

N 3 I	SEX M	STRAIN Beagle	EXPERIMENT 026	TREATMENT 200 mg/kg i.v.- 1 M
----------	----------	------------------	-------------------	----------------------------------



ORGAN

- |               |          |              |         |                  |           |
|---------------|----------|--------------|---------|------------------|-----------|
| 1. BRAIN      | g 71,7   | 6. HEART     | g 67,3  | 11. INTESTINE    | -         |
| 2. HYPOPHYSIS | g 0,133  | 7. STOMACH   | -       | 12. KIDNEYS      | g 49,5    |
| 3. THYMUS     | mg 12800 | 8. LIVER     | g 299,3 | 13. SUPRAR.      | G mg 1200 |
| 4. THYROID    |          | 9. SPLEEN    | g 79,1  | 14. GONADS       | g 3       |
| 5. LUNGS      |          | 10. PANCREAS |         | 15. SEMINAL VES. |           |
|               |          |              |         | 16. PROSTATE OR  |           |
|               |          |              |         | UTERUS           | mg 1300   |

NOTE:

Autoptic:

Histologic:

Date 27/9/76